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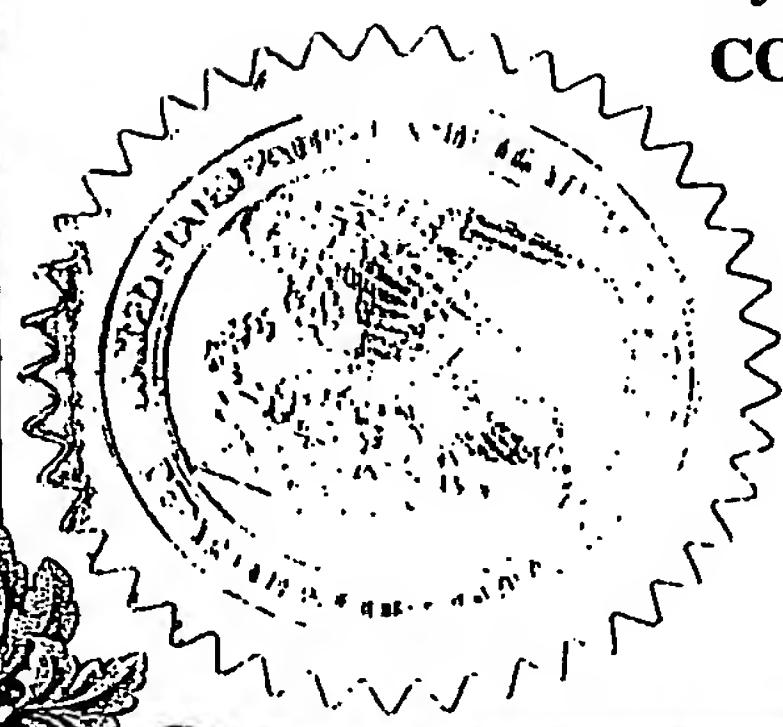
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This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

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TITLE OF THE INVENTION (500 characters max)

CATHEPSIN CYSTEINE PROTEASE INHIBITORS

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE Nicole M. Beeler

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Date 01/08/2004

REGISTRATION NO.
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TITLE OF THE INVENTION
CATHEPSIN CYSTEINE PROTEASE INHIBITORS

BACKGROUND OF THE INVENTION

5 A variety of disorders in humans and other mammals involve or are associated with abnormal bone resorption. Such disorders include, but are not limited to, osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, atherosclerosis, obesity, parasitic infection, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, metastatic 10 bone disease, hypercalcemia of malignancy, and multiple myeloma. One of the most common of these disorders is osteoporosis, which in its most frequent manifestation occurs in postmenopausal women. Osteoporosis is a systemic skeletal disease characterized by a low bone 15 mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Osteoporotic fractures are a major cause of morbidity and mortality in the elderly population. Because osteoporosis, as well as other disorders associated with bone loss, are generally chronic conditions, it is believed that appropriate therapy will typically require chronic treatment.

Bone resorption is primarily performed by osteoclasts, which are multinuclear giant cells. Osteoclasts resorb bone by forming an initial cellular attachment to bone tissue, followed by the formation of an extracellular compartment or lacunae. The lacunae are maintained at a low pH by a proton-ATP pump. The acidified environment in the lacunae allows for initial demineralization of bone followed by the degradation of bone proteins or collagen by proteases such as cysteine proteases. See Delaisse, J. M. *et al.*, 1980, *Biochem J* **192**:365-368; Delaisse, J. *et al.*, 1984, *Biochem Biophys Res Commun*:441-447; Delaisse, J. M. *et al.*, 1987, *Bone* **8**:305-313, which are hereby incorporated by reference in their entirety. Collagen constitutes 95 % of the organic matrix of bone. Therefore, proteases involved in collagen degradation are an essential component of bone turnover, and as a consequence, the development and progression of osteoporosis.

Cathepsins belong to the papain superfamily of cysteine proteases. These proteases function in the normal physiological as well as pathological degradation of connective tissue. Cathepsins play a major role in intracellular protein degradation and turnover and remodeling. To date, a number of cathepsin have been identified and sequenced from a number of sources. These cathepsins are naturally found in a wide variety of tissues. For example, cathepsin B, C, F, H, L, K, O, S, V, W, and Z have been cloned. Cathepsin K (which is also known by the abbreviation cat K) is also known as cathepsin O and cathepsin O2. See PCT

Application WO 96/13523, Khepri Pharmaceuticals, Inc., published May 9, 1996, which is hereby incorporated by reference in its entirety. Cathepsin L is implicated in normal lysosomal proteolysis as well as several diseases states, including, but not limited to, metastasis of melanomas. Cathepsin S is implicated in Alzheimer's disease, asthma, atherosclerosis, chronic 5 obstructive pulmonary disease and certain autoimmune disorders, including, but not limited to juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis and Hashimoto's thyroiditis; allergic disorders, including, but not limited to asthma; and allogenic immune responses, including, but not limited to, rejection of organ transplants or tissue grafts. Increased Cathepsin B levels and 10 redistribution of the enzyme are found in tumors, suggesting a role in tumor invasion and metastasis. In addition, aberrant Cathepsin B activity is implicated in such disease states as rheumatoid arthritis, osteoarthritis, pneumocystis carinii, acute pancreatitis, inflammatory airway disease and bone and joint disorders.

Mammalian cathepsins are related to the papain-like cysteine proteases expressed 15 by disease-causing parasites including those from the families protozoa, platyhelminthes, nematodes and arthropodes. These cysteine proteases play an essential role in the life cycle of these organisms.

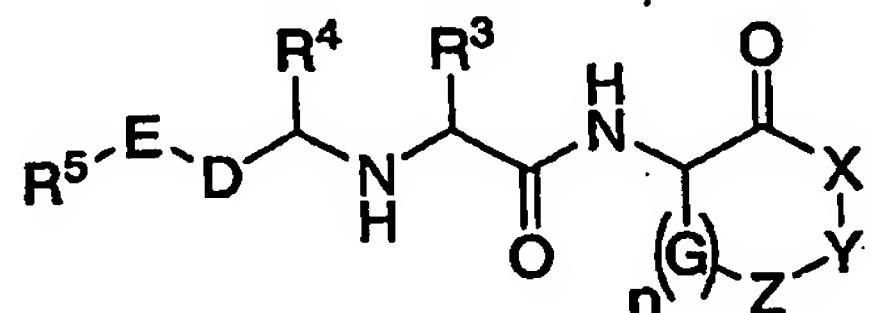
Cysteine protease inhibitors such as E-64 (*trans*-epoxysuccinyl-L-leucylamide-(4-guanidino) butane) are known to be effective in inhibiting bone resorption. See Delaisse, J. M. et 20 al., 1987, *Bone* 8:305-313, which is hereby incorporated by reference in its entirety. Recently, cathepsin K was cloned and found specifically expressed in osteoclasts See Tezuka, K. et al., 1994, *J Biol Chem* 269:1106-1109; Shi, G. P. et al., 1995, *FEBS Lett* 357:129-134; Bromme, D. and Okamoto, K., 1995, *Biol Chem Hoppe Seyler* 376:379-384; Bromme, D. et al., 1996, *J Biol Chem* 271:2126-2132; Drake, F. H. et al., 1996, *J Biol Chem* 271:12511-12516, which are 25 hereby incorporated by reference in their entirety. Concurrent to the cloning, the autosomal recessive disorder, pycnodysostosis, characterized by an osteopetrotic phenotype with a decrease in bone resorption, was mapped to mutations present in the cathepsin K gene. To date, all mutations identified in the cathepsin K gene are known to eliminate collagenase activity. See Gelb, B. D. et al., 1996, *Science* 273:1236-1238; Johnson, M. R. et al., 1996, *Genome Res* 30 6:1050-1055; Hou, W.-S. et al., 1999 *J. Clin. Invest.* 103, 731-738 which are hereby incorporated by reference in their entirety. Therefore, it appears that cathepsin K is involved in osteoclast mediated bone resorption.

Human type I collagen, the major collagen in bone is a good substrate for cathepsin K. See Kafienah, W., et al., 1998, *Biochem J* 331:727-732, which is hereby 35 incorporated by reference in its entirety. Accordingly, inhibitors of Cathepsin K can reduce bone

resorption. Such inhibitors would be useful in treating disorders involving bone resorption, such as osteoporosis.

SUMMARY OF THE INVENTION

5 The present invention relates to compounds that are capable of treating or preventing cathepsin dependent conditions or disease states in a mammal in need thereof. One embodiment of the present invention is illustrated by a compound of Formula I, and the pharmaceutically acceptable salts, esters, stereoisomers and N-oxide derivatives thereof:

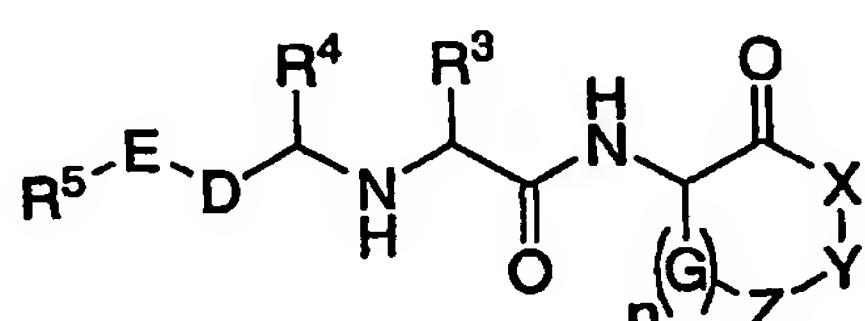


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I.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds of the following chemical formula:



15 wherein X is O or -NR⁹;
 Y is CR¹R², -SO₂, C=O or -NR⁹;
 Z is CR¹R², O, S, -SO₂ or -NR⁹;
 Each G is independently CR¹R²;

20 R¹ is hydrogen, halo, or C₁₋₆ alkyl which is optionally substituted with one, two, or three substituents independently selected from halo or -OR⁸;

R² is hydrogen, halo or C₁₋₆ alkyl which is optionally substituted with one, two, or three substituents independently selected from halo or -OR⁸;

25

or R¹ and R² can be taken together with the carbon atom to which they are attached to form a C₃-8 membered ring which is optionally substituted with one or two substituents independently selected from C₁-6 alkyl, halo or keto;

5 R3 is C1-6 alkyl or C2-6 alkenyl, wherein said alkyl and alkenyl groups are optionally substituted with C3-6 cycloalkyl, aryl, heteroaryl or one to six halo;

R⁴ is C₁₋₆ alkyl substituted with 1-6 halo;

D is aryl or heteroaryl, wherein said aryl or heteroaryl group, which may be monocyclic or
10 bicyclic, is optionally substituted on either the carbon or the heteroatom with one to five
substituents independently selected from C₁-6 alkyl, haloalkyl, halo, keto, alkoxy, -SR⁶, -OR⁶,
N(R⁶)₂ or -SO₂R⁶

E is aryl or heteroaryl, wherein said aryl or heteroaryl group, which may be monocyclic or bicyclic, is optionally substituted on either the carbon or the heteroatom with one to five substituents independently selected from C1-6 alkyl, haloalkyl, halo, keto, alkoxy, -SR⁶, -OR⁶, N(R⁶)₂ or -SO₂R⁶;

N(R⁶)₂ or -SO₂R⁷-,
 R⁵ is hydrogen, C₁₋₆ alkyl, C₁₋₆ alkyloxy, aryl, heteroaryl, C₃₋₈ cycloalkyl, heterocyclyl, -OR⁶,
 -C(O)R⁶, -R⁷C(O)R⁶, -C(O)N(R^a)(R^b), -C(O)N(R⁹)(R⁹), -C(R⁷)(R⁸)OH, R⁷SR⁶, -
 C(R^a)(R^b)N(R⁶)₂, C(R^a)(R^b)N(R^a)(R^b), -NR⁷C(O)NR⁷S(O)R⁶, -SO_mR⁶, -SO₂N(R^a)(R^b),
 -SO₂N(R⁷)C(O)(R⁹), -SO₂(R⁷)C(O)N(R⁹)₂, -N(R⁷)C(O)N(R⁷)(R⁶), -N(R⁷)C(O)R⁶, -
 N(R⁷)C(O)OR⁷, -N(R⁷)SO₂(R⁷), -C(R^a)(R^b)SC(R^a)(R^b)(R⁶), -
 C(R^a)(R^b)NR⁷C(R^a)(R^b)(R⁶), -C(R^a)(R^b)NH₂, -C(R^a)(R^b)C(R^a)(R^b)N(R^a)(R^b), -
 C(O)C(R^a)(R^b)N(R^a)(R^b), -C(R^a)(R^b)N(R⁶)C(O)R⁶, -C(R^a)(R^b)C(O)N(R^a)(R^b), wherein said
 groups are optionally substituted on either the carbon or the heteroatom with one to five
 substituents independently selected from C₁₋₆ alkyl, halo, keto, cyano, haloalkyl, hydroxyalkyl, -
 OR⁶, -NO₂, -NH₂, -NHS(O)R⁸, -R⁶SO₂R⁹, -SO_mR⁷, heterocyclyl, aryl, or heteroaryl;
 20
 25

30 R⁶ is selected from hydrogen, C₁₋₆ alkyl, aryl, aryl(C₁₋₄)alkyl, heteroaryl, heteroaryl(C₁₋₄)alkyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkyl(C₁₋₄)alkyl, and heterocyclyl(C₁₋₄)alkyl wherein said groups can be optionally substituted with one, two, or three substituents independently selected from halo, alkoxy, cyano, -NR^aR^b, -SR^a or -SO_mR^a;

R⁷ is hydrogen or C₁-6 alkyl;

35 R⁸ is hydrogen or C₁₋₆ alkyl;

R⁹ is hydrogen, C₁₋₆ alkyl, C(O)R⁷, C(O)C₁₋₆ alkyl, C(O)aryl, C(O)heteroaryl, C(O)C₁₋₆ alkoxy, SO₂(C₁₋₆ alkyl), SO₂(aryl) or SO₂(heteroaryl), wherein said alkyl groups are optionally substituted with one, two, or three substituents independently selected from halo, alkoxy, cyano, 5 -NR⁷ or -SR⁷;

R^a is hydrogen or C₁₋₆ alkyl which is optionally substituted with one, two, or three substituents independently selected from halo or -OR⁶;

10 R^b is hydrogen or C₁₋₆ alkyl which is optionally substituted with one, two, or three substituents independently selected from halo or -OR⁶;

or R^a and R^b can be taken together with the nitrogen atom to which they are attached or are between them to form a C₃₋₈ heterocycl ring which is optionally substituted with one or two 15 substituents independently selected from C₁₋₆ alkyl, halo hydroxyalkyl, hydroxy, alkoxy or keto;

n is an integer from zero to two;

m is an integer from zero to two;

and the pharmaceutically acceptable salts and stereoisomers thereof, such that the neutral form of the resulting molecule has a molecular weight <1000 daltons.

20. In one class of the invention, R³ is C₁₋₆ alkyl which is optionally substituted with one to six halo.

In another class of the invention, D is aryl. In a subclass of the invention, D is phenyl.

25 In another class of the invention, E is aryl or heteroaryl, wherein said aryl or heteroaryl group is optionally substituted on either the carbon or the heteroatom with one to five halo. In a subclass of the invention, E is phenyl or pyridyl, wherein said phenyl or pyridyl group may be substituted with one to five halo.

Reference to the preferred embodiments set forth above is meant to include all 30 combinations of particular and preferred groups unless stated otherwise.

Specific embodiments of the present invention include, but are not limited to:

N¹-(2-oxotetrahydrofuran-3-yl)-N²-{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide;

N¹-[2-oxo-1-(phenylsulfonyl)pyrrolidin-3-yl]-N²-{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide;

5 N^2 -((1*S*)-1-{4'-[1-(aminocarbonyl)cyclopropyl]biphenyl-4-yl}-2,2-difluoroethyl)-4-fluoro- N^1 -[(3*S,4S*)-2-oxo-4-(trifluoromethyl)pyrrolidin-3-yl]-L-leucinamide;
 N^2 -((1*S*)-2,2-difluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]propyl)-4-fluoro- N^1 -[(3*S*)-2-oxo-4-(trifluoromethyl)tetrahydrofuran-3-yl]-L-leucinamide;
 N^2 -((1*S*)-1-{4'-[1-(aminocarbonyl)cyclopropyl]biphenyl-4-yl}-2,2-difluoroethyl)-4-fluoro- N^1 -[(3*S,4S*)-4-methyl-2-oxo-1-(pyridin-2-ylmethyl)pyrrolidin-3-yl]-L-leucinamide;
 N^2 -((1*S*)-1-{4'-[1-(aminocarbonyl)cyclopropyl]biphenyl-4-yl}-2,2-difluoroethyl)- N^1 -[(3*R*)-4,4-difluoro-2-oxopyrrolidin-3-yl]-4-fluoro-L-leucinamide;
or a pharmaceutically acceptable salt or stereoisomer thereof.

10 Also included within the scope of the present invention is a pharmaceutical composition which is comprised of a compound of Formula I as described above and a pharmaceutically acceptable carrier. The invention is also contemplated to encompass a pharmaceutical composition which is comprised of a pharmaceutically acceptable carrier and any of the compounds specifically disclosed in the present application, alone or in combination with any other disclosed compound. These and other aspects of the invention will be apparent from 15 the teachings contained herein.

Utilities

The compounds of the present invention are inhibitors of cathepsins and are therefore useful to treat or prevent cathepsin dependent diseases or conditions in mammals, preferably humans. Specifically, the compounds of the present invention are selective inhibitors of Cathepsin K in that they are at least 100 fold selective over cathepsins B, L, S and F, and are useful to treat or prevent Cathepsin K dependent diseases or conditions in mammals, preferably humans.

25 “Cathepsin dependent diseases or conditions” refers to pathologic conditions that depend on the activity of one or more cathepsins. “Cathepsin K dependent diseases or conditions” refers to pathologic conditions that depend on the activity of Cathepsin K. Diseases associated with Cathepsin K activities include osteoporosis, glucocorticoid induced osteoporosis, Paget’s disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, atherosclerosis and cancer including metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma. In treating such conditions with the instantly claimed compounds, the required therapeutic amount will vary according to the specific disease and is readily ascertainable by those skilled in the art. Although both treatment and prevention are contemplated by the scope of the invention, the treatment of these conditions is the preferred use.

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An embodiment of the invention is a method of inhibiting cathepsin activity in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

5 A class of the embodiment is the method wherein the cathepsin activity is cathepsin K activity.

Another embodiment of the invention is a method of treating or preventing cathepsin dependent conditions in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

10 A class of the embodiment is the method wherein the cathepsin activity is cathepsin K activity.

Another embodiment of the invention is a method of inhibiting bone loss in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

15 Another embodiment of the invention is a method of reducing bone loss in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. The utility of cathepsin K inhibitors in the inhibition of bone resorption is known in the literature, see Stroup, G.B., Lark, M.W., Veber, D.F., Bhattacharrya, A., Blake, S., Dare, L.C., Erhard, K.F., Hoffman, S.J., James, I.E., Marquis, R.W., Ru, Y., Vasko-Moser, J.A., Smith, B.R., Tomaszek, T. and Gowen, M. Potent and selective inhibition of human cathepsin K leads to inhibition of bone resorption in vivo in a nonhuman primate. *J. Bone Miner. Res.*, 16:1739-1746;2001; and Votta, B.J., Levy, M.A., Badger, A., Dodds, R.A., James, I.E., Thompson, S., Bossard, M.J., Carr, T., Connor, J.R., Tomaszek, T.A., Szewczuk, L., Drake, F.H., Veber, D., and Gowen, M. Peptide aldehyde inhibitors of cathepsin K inhibit bone resorption both in vivo and in vitro. *J. Bone Miner. Res.* 12:1396-1406; 1997.

25 30 Another embodiment of the invention is a method of treating or preventing osteoporosis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the above pharmaceutical compositions described above. The utility of cathepsin K inhibitors in the treatment or prevention of osteoporosis is known in the literature, see Saftig, P., Hunziker, E., Wehmeyer, O., Jones, S., Boyde, A., Rommerskirch, W., Moritz, J.D., Schu, P., and Vonfigura, K. Impaired osteoclast bone resorption leads to osteopetrosis in cathepsin K-deficient mice. *Proc. Natl. Acad. Sci. USA* 95:13453-13458; 1998.

Another embodiment of the invention is a method of treating or preventing rheumatoid arthritic condition in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that progressive destruction of the periarticular bone is a major cause of joint dysfunction and disability in patients with rheumatoid arthritis (RA), see Goldring SR, "Pathogenesis of bone erosions in rheumatoid arthritis". *Curr. Opin. Rheumatol.* 2002; 14: 406-10. Analysis of joint tissues from patients with RA have provided evidence that cathepsin K positive osteoclasts are the cell types that mediate the focal bone resorption associated with rheumatoid synovial lesion, see Hou, W-S, 5 Li, W, Keyszer, G, Weber, E, Levy, R, Klein, MJ, Gravallese, EM, Goldring, SR, Bromme, D, "Comparision of Cathepsin K and S expression within the Rheumatoid and Osteoarthritic Synovium", *Arthritis Rheumatism* 2002; 46: 663-74. In addition, generalized bone loss is a major cause of morbility associated with severe RA. The frequency of hip and spinal fractures is substantially increased in patients with chronic RA, see Gould A, Sambrook, P, Devlin J et al, " 10 15 Osteoclastic activation is the principal mechanism leading to secondary osteoporosis in rheumatoid arthritis". *J. Rheumatol.* 1998; 25: 1282-9. The utility of cathepsin K inhibitors in the treatment or prevention of resorption in subarticular bone and of generalized bone loss represent a rational approach for pharmacological intervention on the progression of rheumatoid arthritis.

Another embodiment of the invention is a method of treating or preventing the progression of osteoarthritis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that osteoarthritis (OA) is accompanied with a well-defined changes in the joints, including erosion of the articular 20 25 cartilage surface, peri-articular endochondral ossification/osteophytosis, and subchondral bony sclerosis and cyst formation, see Oettmeier R, Abendroth, K, "Osteoarthritis and bone: osteologic types of osteoarthritis of the hip", *Skeletal Radiol.* 1989; 18: 165-74. Recently, the potential contribution of subchondral bone sclerosis to the initiation and progression of OA have been suggested. Stiffened subchondral bone as the joint responding to repetitive impulsive 30 35 loading, is less able to attenuate and distribute forces through the joint, subjecting it to greater mechanical stress across the articular cartilage surface. This in turn accelerates cartilage wear and fibrillate, see Radin, EL and Rose RM, "Role of subchondral bone in the initiation and progression of cartilage damage", *Clin. Orthop.* 1986; 213: 34-40. Inhibition of excessive subarticular bone resorption by an anti-resorptive agent such as a cathepsin K inhibitor, will lead to inhibition of subchondral bone turnover, thus may have a favorable impact on OA progression.

In addition to the above hypothesis, cathepsin K protein expression was recently identified in synovial fibroblasts, macrophage-like cells, and chondrocytes from synovium and articular cartilage specimens derived from OA patients, see Hou, W-S, Li, W, Keyszer, G, Weber, E, Levy, R, Klein, MJ, Gravallese, EM, Goldring, SR, Bromme, D, "Comparison of Cathepsin K and S expression within the Rheumatoid and Osteoarthritic Synovium", *Arthritis Rheumatism* 2002; 46: 663-74; and Dodd, RA, Connor, JR, Drake, FH, Gowen, M, "Expression of Cathepsin K messenger RNA in giant cells and their precursors in human osteoarthritic synovial tissues". *Arthritis Rheumatism* 1999; 42: 1588-93; and Konttinen, YT, Mandelin, J, Li, T-F, Salo, J, Lassus, J et al. "Acidic cysteine endoproteinase cathepsin K in the degeneration of the superficial articular hyaline cartilage in osteoarthritis", *Arthritis Rheumatism* 2002; 46: 953-60. These recent studies thus implicated the role of cathepsin K in the destruction of collagen type II in the articular cartilage associated with the progression of osteoarthritis. The utility of cathepsin K inhibitors in the treatment or prevention of osteoarthritis as described in this invention thus comprise of two different mechanisms, one is on the inhibition of osteoclast-driven subchondral bone turnover, and two is on the direct inhibition of collagen type II degeneration in the synovium and cartilage of patients with OA.

Another embodiment of the invention is a method of treating cancer in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that cathepsin K is expressed in human breast carcinoma, prostate cancer and chordoma and has matrix degrading capabilities, see Littlewood-Evans AJ, Bilbe G, Bowler WB, Farley D, Wlodarski B, Kokubo T, Inaoka T, Sloane J, Evans DB, Gallagher JA, "The osteoclast-associated protease cathepsin K is expressed in human breast carcinoma." *Cancer Res* 1997 Dec 1;57(23):5386-90, Brubaker KD, Vessella RL, True LD, Thomas R., Corey E. "Cathepsin K mRNA and protein expression in prostate cancer progression." *J Bone Miner Res* 2003 18, 222-30, Haeckel C, Krueger S, Kuester D, Ostertag H, Samii M, Buehling F, Broemme D, Czerniak B, Roessner A. "Expression of cathepsin K in chordoma." *Hum Pathol* 2000 Jul;31(7):834-40.

Another embodiment of the invention is a method treating atherosclerosis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that cathepsin K is expressed in human atheroma and has significant elastase activity, see Sukhova GK, Shi GP, Simon DI, Chapman HA, Libby P. "Expression of the elastolytic cathepsins S and K in human atheroma and regulation of their production in smooth muscle cells." *J Clin Invest* 1998 Aug 102, 576-83.

Another embodiment of the invention is a method treating obesity in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that cathepsin K mRNA is increased in adipose tissue in several mouse models of obesity and also in adipose tissue of obese human males, see Chiellini C, Costa M, Novelli SE, Amri EZ, Benzi L, Bertacca A, Cohen P, Del Prato S, Friedman JM, Maffei M. "Identification of cathepsin K as a novel marker of adiposity in white adipose tissue." *J Cell Physiol* 2003, 195, 309-21.

5 Another embodiment of the invention is a method of treating parasitic infections in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that mammalian cathepsins are related to the papain-like cysteine proteases which play an important role in the life cycle of these parasites. Such parasites are involved in the diseases of malaria, American trypanosomiasis, African trypanosomiasis, 10 leishmaniasis, giardiasis, trichomoniasis, amoebiasis, schistosomiasis, fascioliasis, paragonimiasis and intestinal roundworms, see Lecaille F, Kaleta J, Bromme D., Human and 15 parasitic papain-like cysteine proteases: their role in physiology and pathology and recent developments in inhibitor design. *Chem Rev* 2002 102, 4459-88.

Another embodiment of the invention is a method of treating mammalian diseases 20 associated with cathepsin S including Alzheimer's disease, atherosclerosis, chronic obstructive pulmonary disease, cancer and certain autoimmune disorders, including, but not limited to juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis and Hashimoto's thyroiditis; allergic disorders, including, but not limited to asthma; and allogenic immune responses, including, but 25 not limited to, rejection of organ transplants or tissue grafts. It is known in the literature that cathepsin S activity is associated with the above disease states, see Munger JS, Haass C, Lemere CA, Shi GP, Wong WS, Teplow DB, Selkoe DJ, Chapman HA. Lysosomal processing of amyloid precursor protein to A beta peptides: a distinct role for cathepsin S. *Biochem J* 1995 311, 299-305, Sukhova GK, Zhang Y, Pan JH, Wada Y, Yamamoto T, Naito M, Kodama T, 30 Tsimikas S, Witztum JL, Lu ML, Sakara Y, Chin MT, Libby P, Shi GP. Deficiency of cathepsin S reduces atherosclerosis in LDL receptor-deficient mice. *J Clin Invest* 2003 111, 897-906, Zheng T, Zhu Z, Wang Z, Homer RJ, Ma B, Riese RJ Jr, Chapman HA Jr, Shapiro SD, Elias JA. Inducible targeting of IL-13 to the adult lung causes matrix metalloproteinase- and cathepsin- 35 dependent emphysema. *J Clin Invest* 2000 106, 1081-93, Shi GP, Sukhova GK, Kuzuya M, Ye Q, Du J, Zhang Y, Pan JH, Lu ML, Cheng XW, Iguchi A, Perrey S, Lee AM, Chapman HA, Libby

P. Deficiency of the cysteine protease cathepsin S impairs microvessel growth. *Circ Res* 2003 92, 493-500, Nakagawa TY, Brissette WH, Lira PD, Griffiths RJ, Petrushova N, Stock J, McNeish JD, Eastman SE, Howard ED, Clarke SR, Rosloniec EF, Elliott EA, Rudensky AY. Impaired invariant chain degradation and antigen presentation and diminished collagen-induced arthritis in cathepsin S null mice. *Immunity* 1999 10,207-17.

5 Exemplifying the invention is the use of any of the compounds described above in the preparation of a medicament for the treatment or prevention of osteoporosis in a mammal in need thereof. Still further exemplifying the invention is the use of any of the compounds described above in the preparation of a medicament for the treatment or prevention of: bone loss, 10 bone resorption, bone fractures, metastatic bone disease or disorders related to cathepsin functioning.

15 The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or 20 parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

25 In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. For oral use of a therapeutic compound according to this invention, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. For oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated 30 into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without 35 limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. When aqueous

5 suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

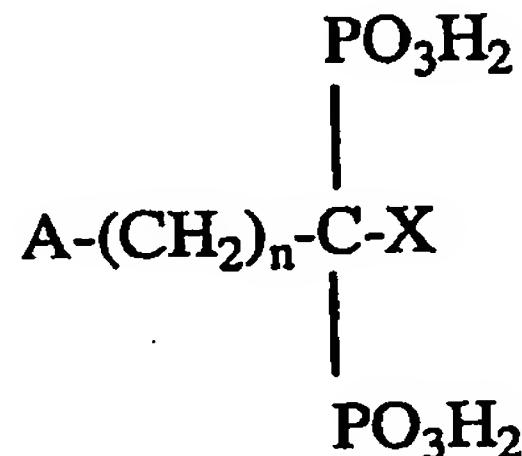
The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxy-ethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polyactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or 20 amphipathic block copolymers of hydrogels.

The instant compounds are also useful in combination with known agents useful for treating or preventing osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, 25 atherosclerosis, obesity, parasitic infection, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma. Combinations of the presently disclosed compounds with other agents useful in treating or preventing osteoporosis or other bone disorders are within the scope of the invention. A person of ordinary skill in the art would be able to discern which combinations of 30 agents would be useful based on the particular characteristics of the drugs and the disease involved. Such agents include the following: an organic bisphosphonate; an estrogen receptor modulator; an androgen receptor modulator; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; an osteoblast anabolic agent, such as PTH; selective cyclooxygenase-2 inhibitor; and the pharmaceutically acceptable salts and 35 mixtures thereof. A preferred combination is a compound of the present invention and an

organic bisphosphonate. Another preferred combination is a compound of the present invention and an estrogen receptor modulator. Another preferred combination is a compound of the present invention and an androgen receptor modulator. Another preferred combination is a compound of the present invention and an osteoblast anabolic agent.

5 "Organic bisphosphonate" includes, but is not limited to, compounds of the chemical formula



wherein n is an integer from 0 to 7 and wherein A and X are independently selected from the group consisting of H, OH, halogen, NH₂, SH, phenyl, C1-C30 alkyl, C3-C30 branched or 10 cycloalkyl, bicyclic ring structure containing two or three N, C1-C30 substituted alkyl, C1-C10 alkyl substituted NH₂, C3-C10 branched or cycloalkyl substituted NH₂, C1-C10 dialkyl substituted NH₂, C1-C10 alkoxy, C1-C10 alkyl substituted thio, thiophenyl, halophenylthio, C1-C10 alkyl substituted phenyl, pyridyl, furanyl, pyrrolidinyl, imidazolyl, imidazopyridinyl, and 15 benzyl, such that both A and X are not selected from H or OH when n is 0; or A and X are taken together with the carbon atom or atoms to which they are attached to form a C3-C10 ring.

In the foregoing chemical formula, the alkyl groups can be straight, branched, or 20 cyclic, provided sufficient atoms are selected for the chemical formula. The C1-C30 substituted alkyl can include a wide variety of substituents, nonlimiting examples which include those selected from the group consisting of phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, NH₂, C1-C10 alkyl or dialkyl substituted NH₂, OH, SH, and C1-C10 alkoxy.

The foregoing chemical formula is also intended to encompass complex carbocyclic, aromatic and hetero atom structures for the A or X substituents, nonlimiting examples of which include naphthyl, quinolyl, isoquinolyl, adamantyl, and chlorophenylthio.

25 Pharmaceutically acceptable salts and derivatives of the bisphosphonates are also useful herein. Non-limiting examples of salts include those selected from the group consisting alkali metal, alkaline metal, ammonium, and mono-, di-, tri-, or tetra-C1-C30-alkyl-substituted ammonium. Preferred salts are those selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts. More preferred are sodium salts. Non-limiting

examples of derivatives include those selected from the group consisting of esters, hydrates, and amides.

It should be noted that the terms "bisphosphonate" and "bisphosphonates", as used herein in referring to the therapeutic agents of the present invention are meant to also encompass 5 diphosphonates, biphosphonic acids, and diphosphonic acids, as well as salts and derivatives of these materials. The use of a specific nomenclature in referring to the bisphosphonate or bisphosphonates is not meant to limit the scope of the present invention, unless specifically indicated. Because of the mixed nomenclature currently in use by those of ordinary skill in the art, reference to a specific weight or percentage of a bisphosphonate compound in the present 10 invention is on an acid active weight basis, unless indicated otherwise herein. For example, the phrase "about 5 mg of a bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an alendronate acid active weight basis" means that the amount of the bisphosphonate compound selected is calculated based on 5 mg of alendronate acid.

15 Non-limiting examples of bisphosphonates useful herein include the following:

Alendronate (also known as alendronate sodium or alendronate monosodium trihydrate), 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate.

Alendronate and alendronate are described in U.S. Patents 4,922,007, to

20 Kieczykowski et al., issued May 1, 1990; 5,019,651, to Kieczykowski et al., issued May 28, 1991; 5,510,517, to Dauer et al., issued April 23, 1996; 5,648,491, to Dauer et al., issued July 15, 1997, all of which are incorporated by reference herein in their entirety.

25 Cycloheptylaminomethylene-1,1-bisphosphonic acid, YM 175, Yamanouchi (incadronate, formerly known as cimadronate), as described in U.S. Patent 4,970,335, to Isomura et al., issued November 13, 1990, which is incorporated by reference herein in its entirety.

1,1-dichloromethylene-1,1-diphosphonic acid (clodronic acid), and the disodium salt (clodronate, Procter and Gamble), are described in Belgium Patent 672,205 (1966) and *J. Org. Chem.* 32, 4111 (1967), both of which are incorporated by reference herein in their entirety.

30 1-hydroxy-3-(1-pyrrolidinyl)-propylidene-1,1-bisphosphonic acid (EB-1053).

1-hydroxyethane-1,1-diphosphonic acid (etidronic acid).

35 1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid, also known as BM-210955, Boehringer-Mannheim (ibandronate), is described in U.S. Patent No. 4,927,814, issued May 22, 1990, which is incorporated by reference herein in its entirety.

1-hydroxy-2-imidazo-(1,2-a)pyridin-3-ethylidene (minodronate).

6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate).

3-(dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid (olpadronate).
3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronate).
[2-(2-pyridinyl)ethylidene]-1,1-bisphosphonic acid (piridronate) is described in
U.S. Patent No. 4,761,406, which is incorporated by reference in its entirety.

5 1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid (risedronate).
(4-chlorophenyl)thiomethane-1,1-disphosphonic acid (tiludronate) as described in
U.S. Patent 4,876,248, to Breliere et al., October 24, 1989, which is incorporated by reference
herein in its entirety.

10 1-hydroxy-2-(1H-imidazol-1-yl)ethylidene-1,1-bisphosphonic acid (zoledronate).
Nonlimiting examples of bisphosphonates include alendronate, cimadronate,
clodronate, etidronate, ibandronate, incadronate, minodronate, neridronate, olpadronate,
pamidronate, piridronate, risedronate, tiludronate, and zolendronate, and pharmaceutically
acceptable salts and esters thereof. A particularly preferred bisphosphonate is alendronate,
especially a sodium, potassium, calcium, magnesium or ammonium salt of alendronic acid.

15 Exemplifying the preferred bisphosphonate is a sodium salt of alendronic acid, especially a
hydrated sodium salt of alendronic acid. The salt can be hydrated with a whole number of moles
of water or non whole numbers of moles of water. Further exemplifying the preferred
bisphosphonate is a hydrated sodium salt of alendronic acid, especially when the hydrated salt is
alendronate monosodium trihydrate.

20 It is recognized that mixtures of two or more of the bisphosphonate actives can be
utilized.

25 The precise dosage of the organic bisphosphonate will vary with the dosing
schedule, the particular bisphosphonate chosen, the age, size, sex and condition of the mammal
or human, the nature and severity of the disorder to be treated, and other relevant medical and
physical factors. Thus, a precise pharmaceutically effective amount cannot be specified in
advance and can be readily determined by the caregiver or clinician. Appropriate amounts can be
determined by routine experimentation from animal models and human clinical studies.
Generally, an appropriate amount of bisphosphonate is chosen to obtain a bone resorption
inhibiting effect, i.e. a bone resorption inhibiting amount of the bisphosphonate is administered.

30 For humans, an effective oral dose of bisphosphonate is typically from about 1.5 to about 6000
 $\mu\text{g}/\text{kg}$ body weight and preferably about 10 to about 2000 $\mu\text{g}/\text{kg}$ of body weight. For alendronate
monosodium trihydrate, common human doses which are administered are generally in the range
of about 2 mg/day to about 40 mg/day, preferably about 5 mg/day to about 40 mg/day. In the
U.S. presently approved dosages for alendronate monosodium trihydrate are 5 mg/day for

preventing osteoporosis, 10 mg/day for treating osteoporosis, and 40 mg/day for treating Paget's disease.

5 In alternative dosing regimens, the bisphosphonate can be administered at intervals other than daily, for example once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. In a once weekly dosing regimen, alendronate monosodium trihydrate would be administered at dosages of 35 mg/week or 70 mg/week.

10 "Selective estrogen receptor modulators" refers to compounds which interfere or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, estrogen, progestogen, estradiol, droloxifene, raloxifene, lasofoxifene, TSE-424, tamoxifen, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

15 An "estrogen receptor beta modulator" is a compound that selectively agonizes or antagonizes estrogen receptor beta (ER β). Agonizing ER β increases transcription of the tryptophan hydroxylase gene (TPH, the key enzyme in serotonin synthesis) via an ER β mediated event. Examples of estrogen receptor beta agonists can be found in PCT International publication WO 01/82923, which published on November 08, 2001, and WO 02/41835, which published on May 20, 2002, both of which are hereby incorporated by reference in their entirety.

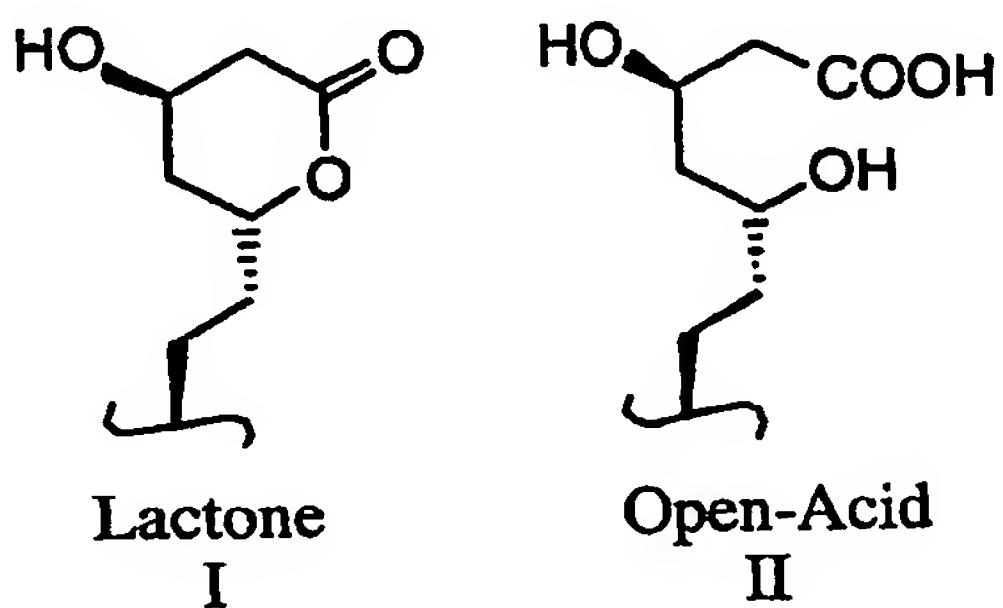
20 "Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5 α -reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

25 "An inhibitor of osteoclast proton ATPase" refers to an inhibitor of the proton ATPase, which is found on the apical membrane of the osteoclast, and has been reported to play a significant role in the bone resorption process. This proton pump represents an attractive target for the design of inhibitors of bone resorption which are potentially useful for the treatment and prevention of osteoporosis and related metabolic diseases. See C. Farina et al., "Selective inhibitors of the osteoclast vacuolar proton ATPase as novel bone antiresorptive agents," DDT, 4: 163-172 (1999), which is hereby incorporated by reference in its entirety.

30 "HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33. The

terms "HMG-CoA reductase inhibitor" and "inhibitor of HMG-CoA reductase" have the same meaning when used herein.

Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see U.S. Patent Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Patent Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®; see U.S. Patent Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see U.S. Patent Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896), atorvastatin (LIPITOR®; see U.S. Patent Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952) and cerivastatin (also known as rivastatin and BAYCHOL®; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefore the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention. An illustration of the lactone portion and its corresponding open-acid form is shown below as structures I and II.



20 In HMG-CoA reductase inhibitors where an open-acid form can exist, salt and ester forms may preferably be formed from the open-acid, and all such forms are included within the meaning of the term "HMG-CoA reductase inhibitor" as used herein. Preferably, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin, and most preferably simvastatin. Herein, the term "pharmaceutically acceptable salts" with respect to the HMG-CoA reductase inhibitor shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as

ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenz-imidazole, diethylamine, piperazine, and tris(hydroxymethyl) aminomethane. Further examples of salt forms of HMG-CoA reductase inhibitors may include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclolate, tosylate, triethiodide, and valerate.

Ester derivatives of the described HMG-CoA reductase inhibitor compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

As used above, "integrin receptor antagonists" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. H.N. Lode and coworkers in PNAS USA 96: 1591-1596 (1999) have observed synergistic effects between an antiangiogenic α_v integrin antagonist and a tumor-specific antibody-cytokine (interleukin-2) fusion protein in the eradication of spontaneous tumor metastases. Their results suggested this combination as having potential for the treatment of cancer and metastatic tumor growth. $\alpha_v\beta_3$ integrin receptor antagonists inhibit bone resorption through a new mechanism distinct from that of all currently available drugs. Integrins are heterodimeric transmembrane adhesion receptors that mediate cell-cell and cell-matrix interactions. The α and β integrin subunits interact non-covalently and bind extracellular matrix ligands in a divalent cation-dependent manner. The most abundant integrin on osteoclasts is $\alpha_v\beta_3$ ($>10^7$ /osteoclast), which appears to play a rate-limiting role in cytoskeletal organization important for cell migration and

polarization. The $\alpha_1\beta_3$ antagonizing effect is selected from inhibition of bone resorption, inhibition of restenosis, inhibition of macular degeneration, inhibition of arthritis, and inhibition of cancer and metastatic growth.

5 "An osteoblast anabolic agent" refers to agents that build bone, such as PTH. The intermittent administration of parathyroid hormone (PTH) or its amino-terminal fragments and analogues have been shown to prevent, arrest, partially reverse bone loss and stimulate bone formation in animals and humans. For a discussion refer to D.W. Dempster et al., "Anabolic actions of parathyroid hormone on bone," *Endocr Rev* 14: 690-709 (1993). Studies have demonstrated the clinical benefits of parathyroid hormone in stimulating bone formation and thereby increasing bone mass and strength. Results were reported by RM Neer et al., in *New Eng J Med* 344 1434-1441 (2001).

10 In addition, parathyroid hormone-related protein fragments or analogues, such as PTHrP-(1-36) have demonstrated potent anticalciuric effects [see M.A. Syed et al., "Parathyroid hormone-related protein-(1-36) stimulates renal tubular calcium reabsorption in normal human 15 volunteers: implications for the pathogenesis of humoral hypercalcemia of malignancy," *JCEM* 86: 1525-1531 (2001)] and may also have potential as anabolic agents for treating osteoporosis.

20 "A selective cyclooxygenase-2 inhibitor," or COX-2 inhibitor, refers to a type of nonsteroidal anti-inflammatory drug (NSAID), that inhibit the with the COX-2 coenzyme, which contributes to pain and inflammation in the body. Nonlimiting examples of COX-2 inhibitors include: celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib.

25 If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

30 The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents. The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of 35 the present invention, the term "administering" shall encompass the treatment of the various

conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," ed. H. 5 Bundgaard, Elsevier, 1985, which is incorporated by reference herein in its entirety. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which 10 results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor 15 or other clinician.

The terms "treating" or "treatment" of a disease as used herein includes: preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease; inhibiting the disease, i.e., arresting or reducing the 20 development of the disease or its clinical symptoms; or relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

The term "bone resorption," as used herein, refers to the process by which osteoclasts degrade bone.

The present invention also encompasses a pharmaceutical composition useful in 25 the treatment of osteoporosis or other bone disorders, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's 30 bloodstream by local bolus injection.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for a cathepsin dependent condition. Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably, from about 1 mg to about 100 mg of active ingredient.

5 Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or

10 15 via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

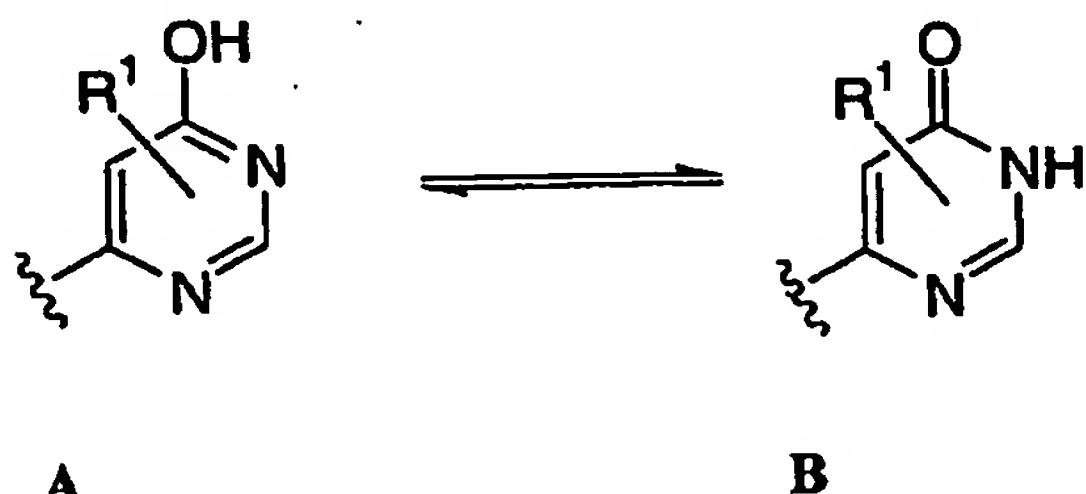
The compounds of the present invention can be used in combination with other agents useful for treating cathepsin-mediated conditions. The individual components of such combinations can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. It will be understood that the scope of combinations of the compounds of this invention with other agents useful for treating cathepsin-mediated conditions includes in principle any combination with any pharmaceutical composition useful for treating disorders related to estrogen functioning.

The scope of the invention therefore encompasses the use of the instantly claimed compounds in combination with a second agent selected from: an organic bisphosphonate; an estrogen receptor modulator; an androgen receptor modulator; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; an osteoblast anabolic agent, such as PTH; a selective cyclooxygenase-2 inhibitor; and the pharmaceutically acceptable salts and mixtures thereof.

These and other aspects of the invention will be apparent from the teachings contained herein.

Definitions

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, 5 racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, being included in the present invention. In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is 10 depicted. For example, any claim to compound A below is understood to include tautomeric structure B, and vice versa, as well as mixtures thereof.



When any variable (e.g. R₁, R₂, Ra etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn into the ring systems from substituents indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms. If the ring system is polycyclic, it is intended that the bond be attached to any of the suitable carbon atoms on the proximal ring only.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results. The phrase "optionally substituted with one or more substituents" should be taken to be equivalent to the phrase "optionally substituted with at least one substituent" and in such cases the preferred embodiment will have from zero to three substituents.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having one to ten carbon atoms unless otherwise specified. For example, C₁-C₁₀, as in "C₁-C₁₀ alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear, branched, or cyclic arrangement. For example, "C₁-C₁₀ alkyl" specifically includes methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on.

"Alkoxy" or "alkyloxy" represents an alkyl group as defined above, unless otherwise indicated, wherein said alkyl group is attached through an oxygen bridge. Examples of alkoxy include methoxy, ethoxy and the like.

The term "cycloalkyl" or "carbocycle" shall mean cyclic rings of alkanes of three to eight total carbon atoms, unless otherwise indicated, or any number within this range (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl).

If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight or branched, containing from 2 to 10 carbon atoms and at least 1 carbon to carbon double bond. Preferably 1 carbon to carbon double bond is present, and up to 4 non-aromatic carbon-carbon double bonds may be present. Thus, "C₂-C₆ alkenyl" means an alkenyl radical having from 2 to 6 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

In certain instances, substituents may be defined with a range of carbons that includes zero, such as (C₀-C₆)alkylene-aryl. If aryl is taken to be phenyl, this definition would include phenyl itself as well as -CH₂Ph, -CH₂CH₂Ph, CH(CH₃)CH₂CH(CH₃)Ph, and so on.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 12 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

The term "heteroaryl", as used herein, represents a stable monocyclic, bicyclic or tricyclic ring of up to 10 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: benzimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl,

oxazoline, isoxazoline, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolyl, quinoxaliny, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydroindolyl, dihydroquinolinyl, 5 methylenedioxybenzene, benzothiazolyl, benzothienyl, quinolinyl, isoquinolinyl, oxazolyl, and tetra-hydroquinoline. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively. If the heteroaryl contains nitrogen atoms, it is understood that the corresponding N-oxides thereof are also encompassed by this definition.

10 As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo. The term "keto" means carbonyl (C=O). The term "haloalkyl" means an alkyl radical as defined above, unless otherwise specified, that is substituted with one to five, preferably one to three halogen. Representative examples include, but are not limited to trifluoromethyl, dichloroethyl, and the like.

15 The term "haloalkoxy" represents a radical -OR where R is alkyl as defined above that is substituted with one to five, preferably one to three halogen. Representative examples include, but are not limited to trifluoromethoxy, dichloroethoxy, and the like.

20 The term "arylalkyl" includes an alkyl portion where alkyl is as defined above and to include an aryl portion where aryl is as defined above. Examples of arylalkyl include, but are not limited to, benzyl, fluorobenzyl, chlorobenzyl, phenylethyl, phenylpropyl, fluorophenylethyl, and chlorophenylethyl. Examples of alkylaryl include, but are not limited to, toluyl, ethylphenyl, and propylphenyl.

25 The term "heteroarylalkyl" as used herein, shall refer to a system that includes a heteroaryl portion, where heteroaryl is as defined above, and contains an alkyl portion. Examples of heteroarylalkyl include, but are not limited to, thienylmethyl, thienylethyl, thienylpropyl, pyridylmethyl, pyridylethyl and imidazoylmethyl.

30 The term "cycloalkylalkyl" includes an alkyl portion where alkyl is as defined above and also includes an cycloalkyl portion where cycloalkyl is as defined above. Examples of cycloalkylalkyl include, but are not limited to, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopropylethyl, and the like.

The term "heterocycloalkylalkyl" includes an alkyl portion where alkyl is as defined above and also includes a heterocycloalkyl portion where heterocycloalkyl is as defined above. Examples of heterocycloalkylalkyl include, but are not limited to, morpholinylmethyl, piperazinylmethyl, pyrrolidinylmethyl, and the like.

The term "hydroxylalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with one or two hydroxy groups, provided that if two hydroxy groups are present they are not both on the same carbon atom. Representative examples include, but are not limited to, 5 hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, and the like.

The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 5- to 10-membered nonaromatic ring, unless otherwise specified, containing from 1 to 4 heteroatoms selected from the group consisting of O, N, S, SO, or SO₂ and includes bicyclic groups. "Heterocyclyl" therefore includes, but is not limited to the following: piperazinyl, 10 piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, dihydropiperidinyl, tetrahydrothiophenyl and the like. If the heterocycle contains a nitrogen, it is understood that the corresponding N-oxides thereof are also encompassed by this definition.

The present invention also includes N-oxide derivatives and protected derivatives of compounds of Formula I. For example, when compounds of Formula I contain an oxidizable nitrogen atom, the nitrogen atom can be converted to an N-oxide by methods well known in the art. Also when compounds of Formula I contain groups such as hydroxy, carboxy, thiol or any group containing a nitrogen atom(s), these groups can be protected with a suitable protecting groups. A comprehensive list of suitable protective groups can be found in T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, Inc. 1981, the disclosure of which is incorporated herein by reference in its entirety. The protected derivatives of compounds of 20 Formula I can be prepared by methods well known in the art.

Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., aryl C₀₋₈ alkyl) it shall be interpreted as including those limitations given above for "alkyl" and "aryl." Designated numbers of carbon atoms (e.g., C₁₋₁₀) shall refer 25 independently to the number of carbon atoms in an alkyl or cyclic alkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed inorganic or 30 organic acids. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, 35 benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like. The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable

salts is more fully described by Berg *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977;66:1-19, hereby incorporated by reference. The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds 5 are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

For purposes of this specification, the following abbreviations have the indicated 10 meanings:

| | | |
|--------------------------------|---|--|
| Ba(OH) ₂ | = | barium hydroxide |
| CDI | = | carbonyl diimidazole |
| CrO ₃ | = | chromium oxide |
| 15 DMF | = | N,N-dimethylformamide |
| EDC | = | Ethyldiethylaminopropylcarbodiimide |
| Et ₃ N | = | triethylamine |
| EtOH | = | ethanol |
| HATU | = | o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium |
| 20 | | hexafluorophosphate |
| H ₅ IO ₆ | = | periodic acid |
| KHMDS | = | potassium hexamethyldisilazane |
| LDA | = | lithium diisopropylamide |
| LiCl | = | lithium chloride |
| 25 LiOH | = | lithium hydroxide |
| MgSO ₄ | = | magnesium sulfide |
| NaBH ₄ | = | sodium borohydride |
| NaClO | = | sodium perchlorate |
| NaOH | = | sodium hydroxide |
| 30 NH ₄ Cl | = | ammonium chloride |
| Pd/C | = | palladium on carbon |
| PdCl ₂ (dppf) | = | [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) |
| PG | = | protecting group |
| iPr ₂ EtN | = | diisopropylethylamine |
| 35 PyBOP | = | benzotriazol-1-yloxytris(pyrrolidino)phosphonium-hexafluorophosphate |

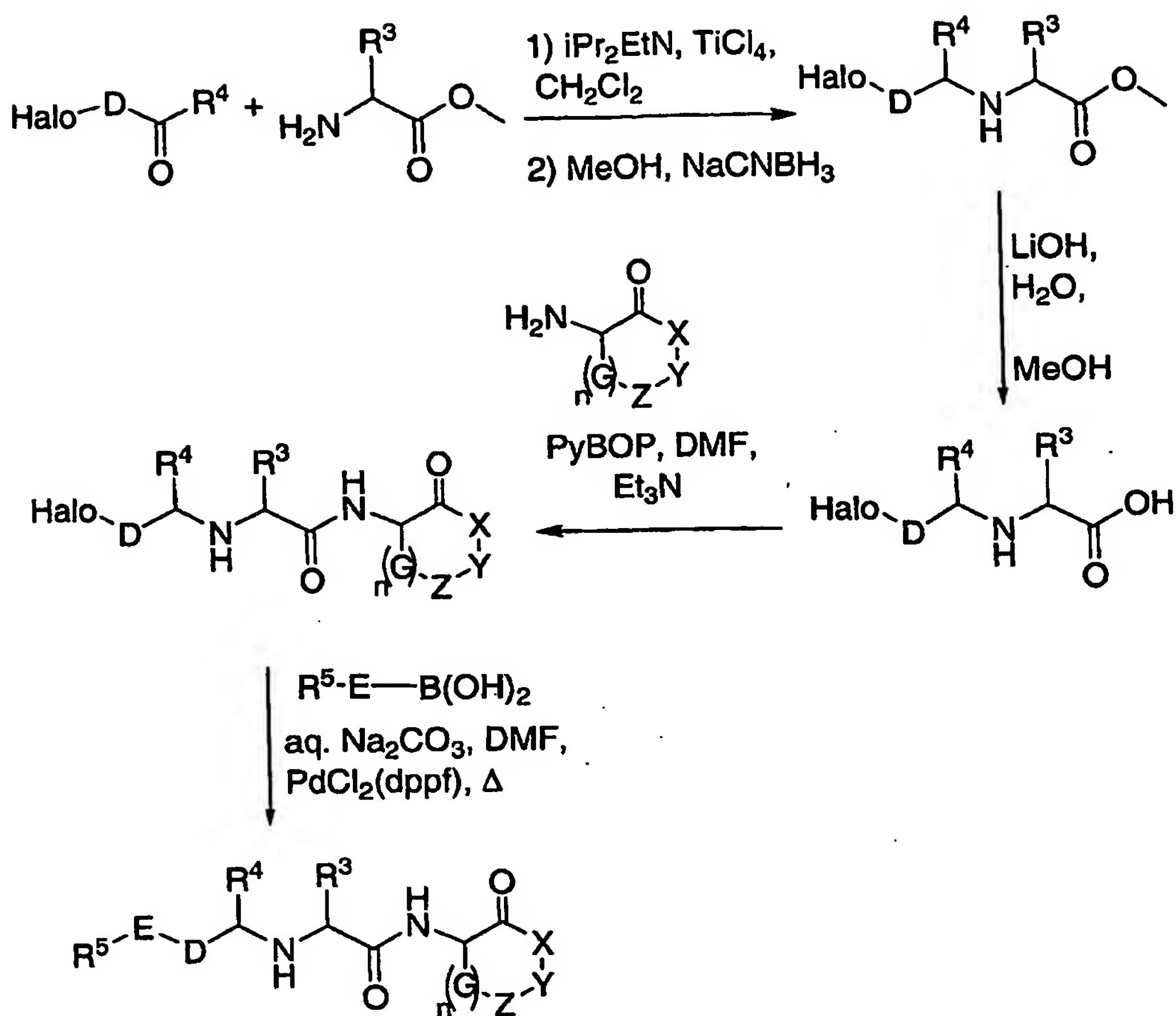
| | | |
|---------------------|---|---------------------------|
| rt | = | room temperature |
| sat. aq. | = | saturated aqueous |
| SiO ₂ | = | silica dioxide |
| THF | = | tetrahydrofuran |
| 5 TiCl ₄ | = | titanium(IV) chloride |
| tlc | = | thin layer chromatography |
| Me | = | methyl |
| Et | = | ethyl |

10 The novel compounds of the present invention can be prepared according to the following general procedures using appropriate materials and are further exemplified by the following specific examples. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the invention. The following example 15 further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless otherwise noted.

20 **SCHEMES**

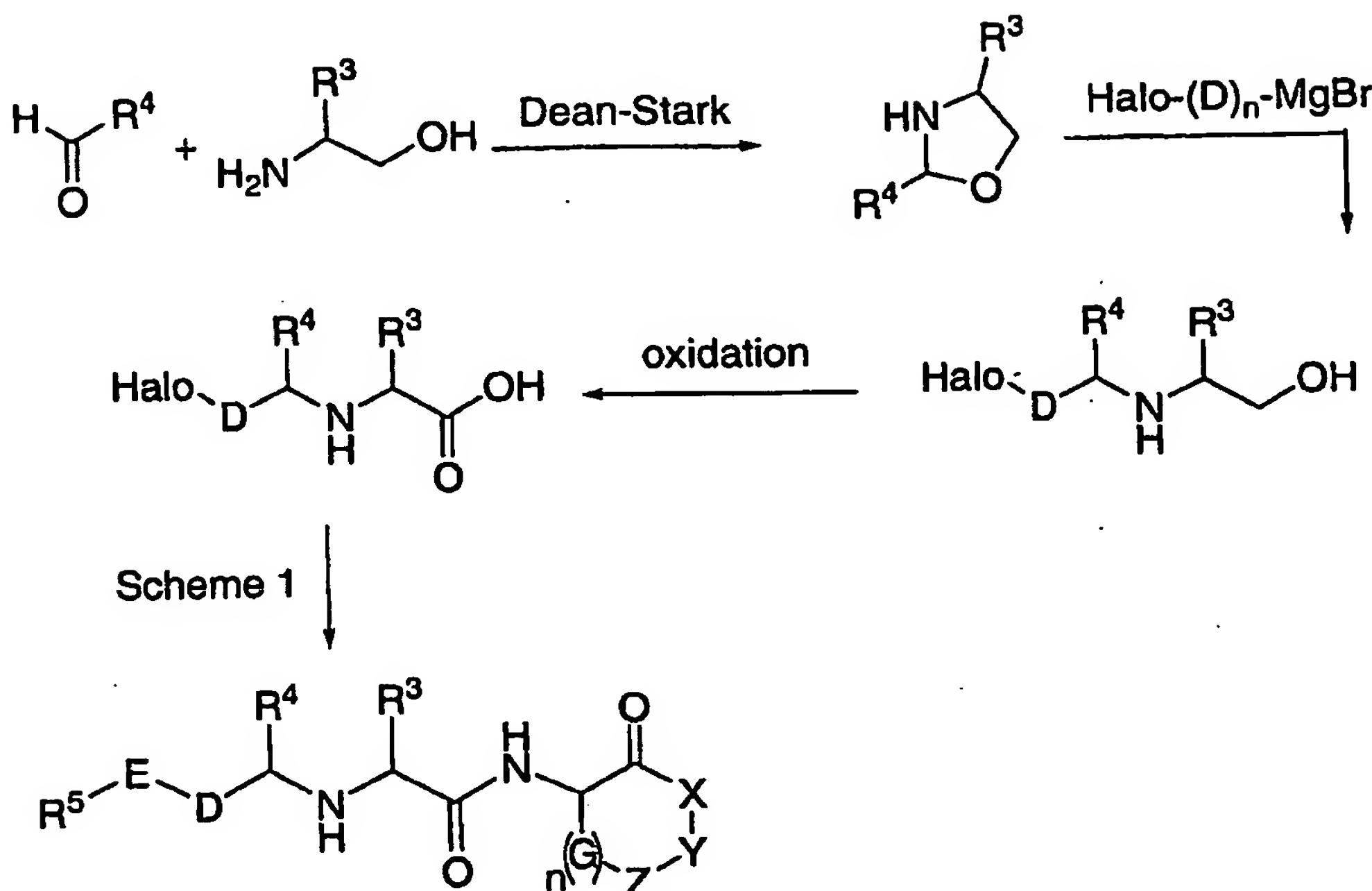
Compounds of the present invention can be prepared according to Scheme 1, as indicated below. Thus an α -amino ester may be added to a haloalkyl ketone to form an aminal which may be dehydrated to an imine in the presence of a dehydrating agent such as TiCl_4 , MgSO_4 or isopropyl trifluoroacetate. Reduction of the imine with a reducing agent such as sodium cyanoborohydride or sodium borohydride provides the amine. Alternatively, a chiral catalyst could be used in this reduction to generate the appropriate chirality at the R^4 stereocenter. Ester hydrolysis and amide formation with an appropriately substituted aminolactam or aminolactone provides the amide derivative. If the substituent on D system is a halogen, a palladium-catalyzed Suzuki coupling with an appropriate boronic acid provides additional compounds of the current invention.

SCHEME 1



Compounds of the present invention may also be prepared according to Scheme 2, as indicated below. A ketone or aldehyde (or its hemiacetal) may be condensed with an amino alcohol to give a cyclic aminal. Treatment with 3 equivalents of a Grignard reagent or organolithium reagent will provide the appropriate alkylated amino alcohol. Oxidation of the alcohol with a chromium system such as a Jones oxidation or H_5IO_6/CrO_3 , or alternatively by a two-step oxidation (eg oxalyl chloride/ DMSO/Et₃N followed by NaClO) will provide the corresponding carboxylic acid. Peptide coupling and Suzuki reaction as described in Scheme 1 will provide compounds of the current invention.

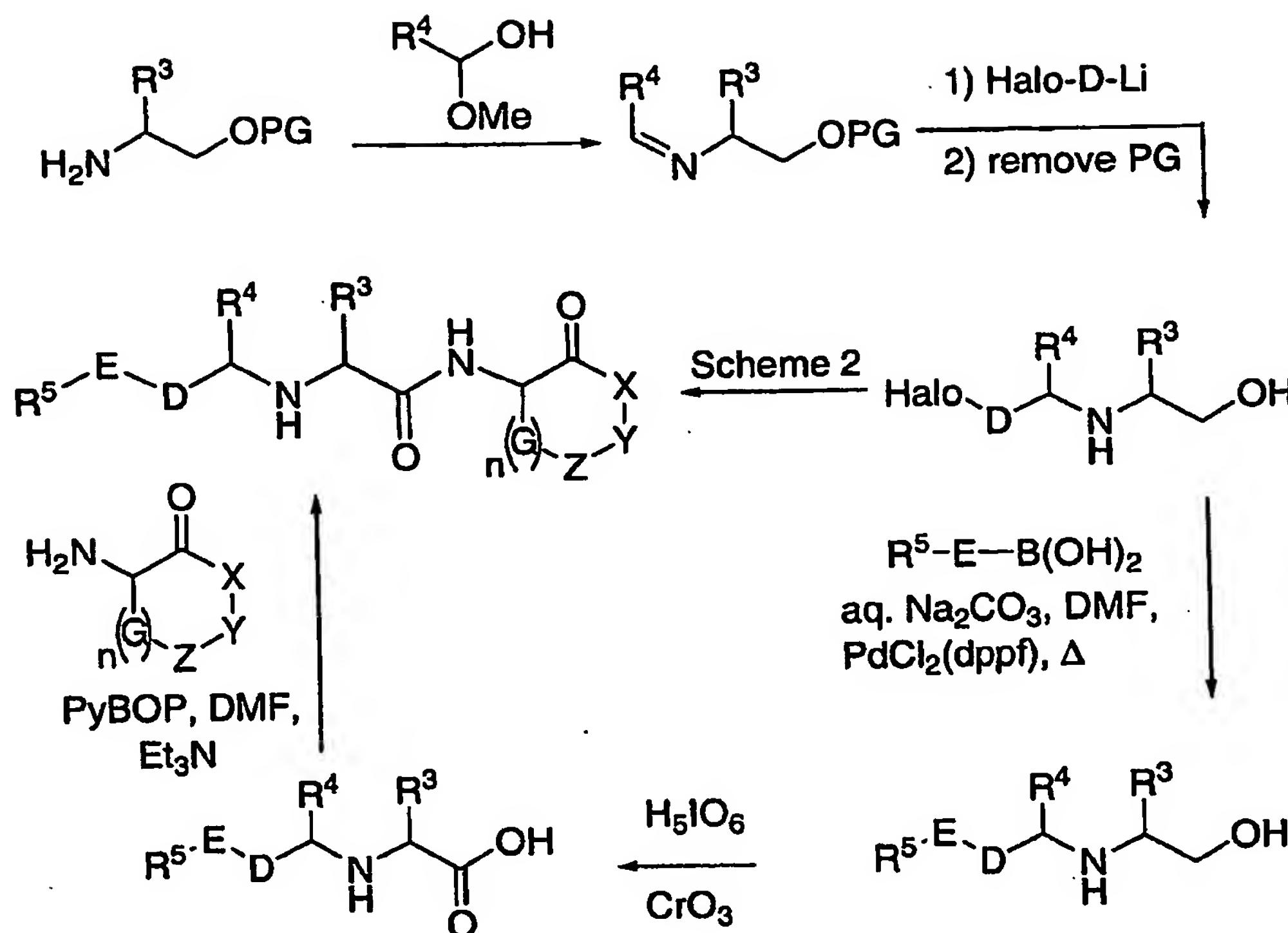
SCHEME 2



5 Compounds of the current invention may also be prepared according to Scheme 3, as indicated below. A hemiacetal may be condensed with an amino alcohol in which the alcohol moiety is protected with a suitable protecting group. Treatment of the resulting imine with a Grignard reagent or organolithium reagent will provide the appropriate alkylated amino alcohol. The alcohol protecting group can then be removed and the alcohol can be converted into compounds of the current invention either by the method described in Scheme 2 or by first conducting the Suzuki reaction, followed by oxidizing the alcohol with H_5IO_6 / CrO_3 and then peptide coupling and oxidation to the ketone.

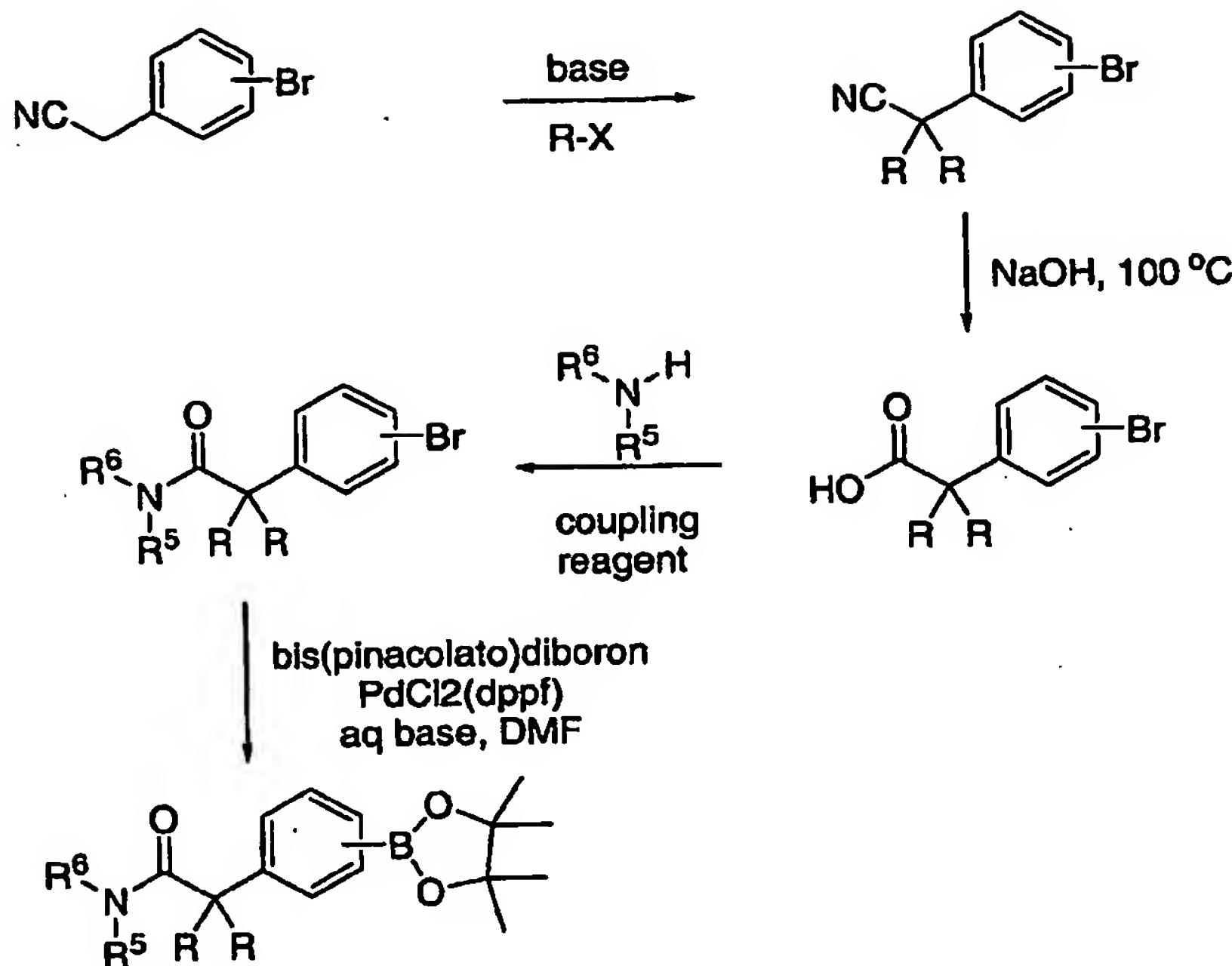
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SCHEME 3



Carboxylamide-aryl bromides used to make compounds of the current invention may be prepared as shown in Scheme 4. Treatment of a bromophenylacetonitrile with a base such as LDA or KHMDS followed by treatment with an alkyl halide such as methyl iodide or 1-bromo-2-chloroethane gives alpha-substituted benzonitriles. Alternatively, this alkylation may be carried out under phase transfer conditions using sodium hydroxide, the alkyl halide and a suitable phase transfer catalyst such as benzyltriethylammonium chloride. Hydrolysis of the nitrile under basic conditions provides the corresponding carboxylic acid which can be coupled with ammonia or a primary or secondary amine using an appropriate coupling reagent such as EDC, CDI, HATU, pyBOP or isobutylchloroformate. This substituted aryl bromide may be coupled with an arylboron pinacolate as described in Scheme 8 to give compounds of the current invention. Alternatively, the aryl bromide may itself be converted into an arylboron pinacolate by a palladium-catalyzed reaction with bis(pinacolato)diboron. This resulting arylboron pinacolate may be used in the Suzuki coupling reactions shown in Schemes 1, 2, or 3 to provide compounds of the current invention.

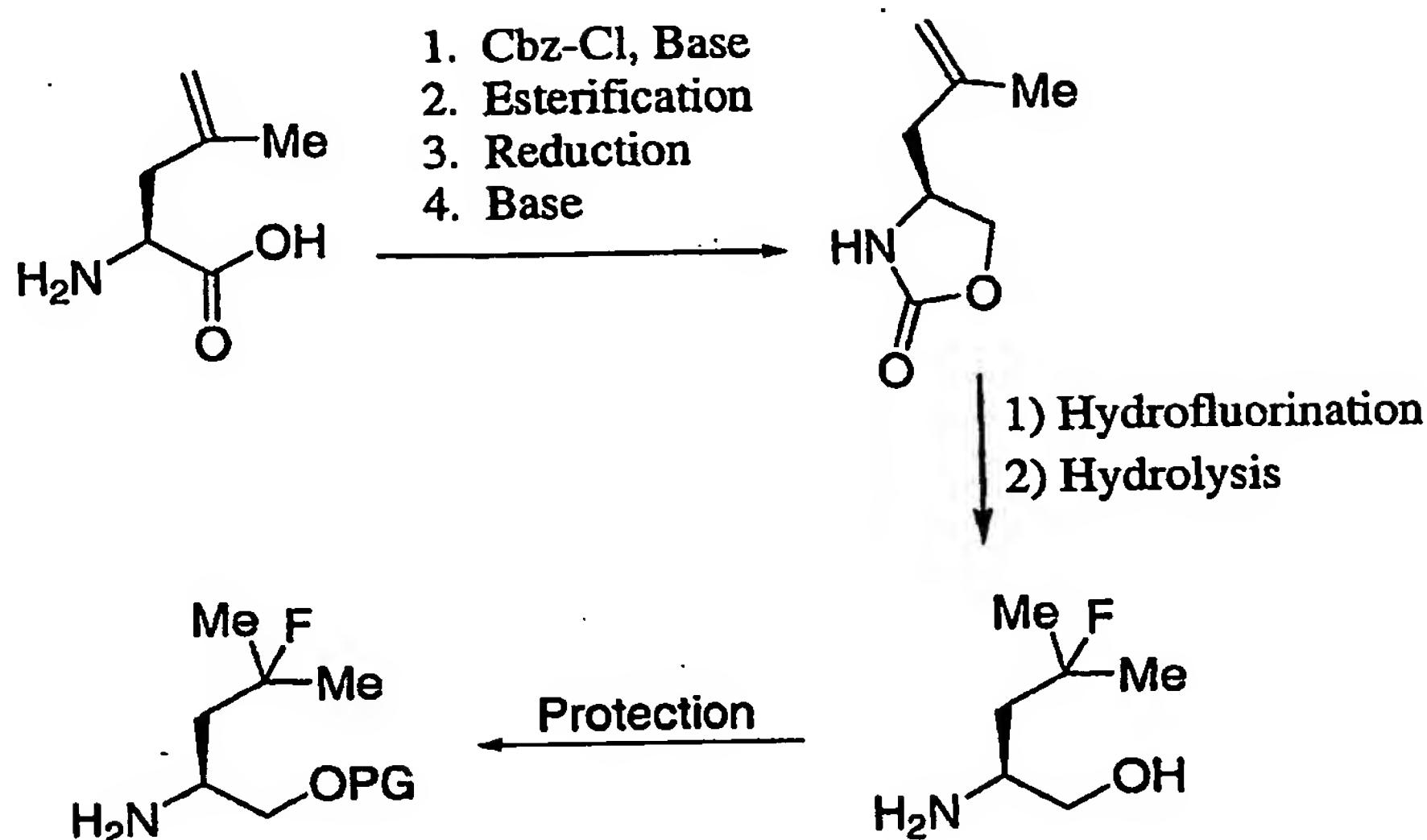
SCHEME 4



5

The 4-fluoroleucinol may be synthesized according to Scheme 5. 4,5-Dehydroleucine is converted to (4*S*)-4-(2-methylprop-2-enyl)-1,3-oxazolidin-2-one as described in the scheme below. This intermediate is then treated with a hydrofluorination reagent such as HF-pyridine to give (4*S*)-4-(2-fluoro-2-methylpropyl)-1,3-oxazolidin-2-one. Basic hydrolysis (i.e. Ba(OH)₂ or 10 NaOH) then affords (2*S*)-2-amino-4-fluoro-4-methylpentan-1-ol, which may be used as shown in Scheme 2. Selective protection of the alcohol provides an intermediate that can be used in Scheme 3.

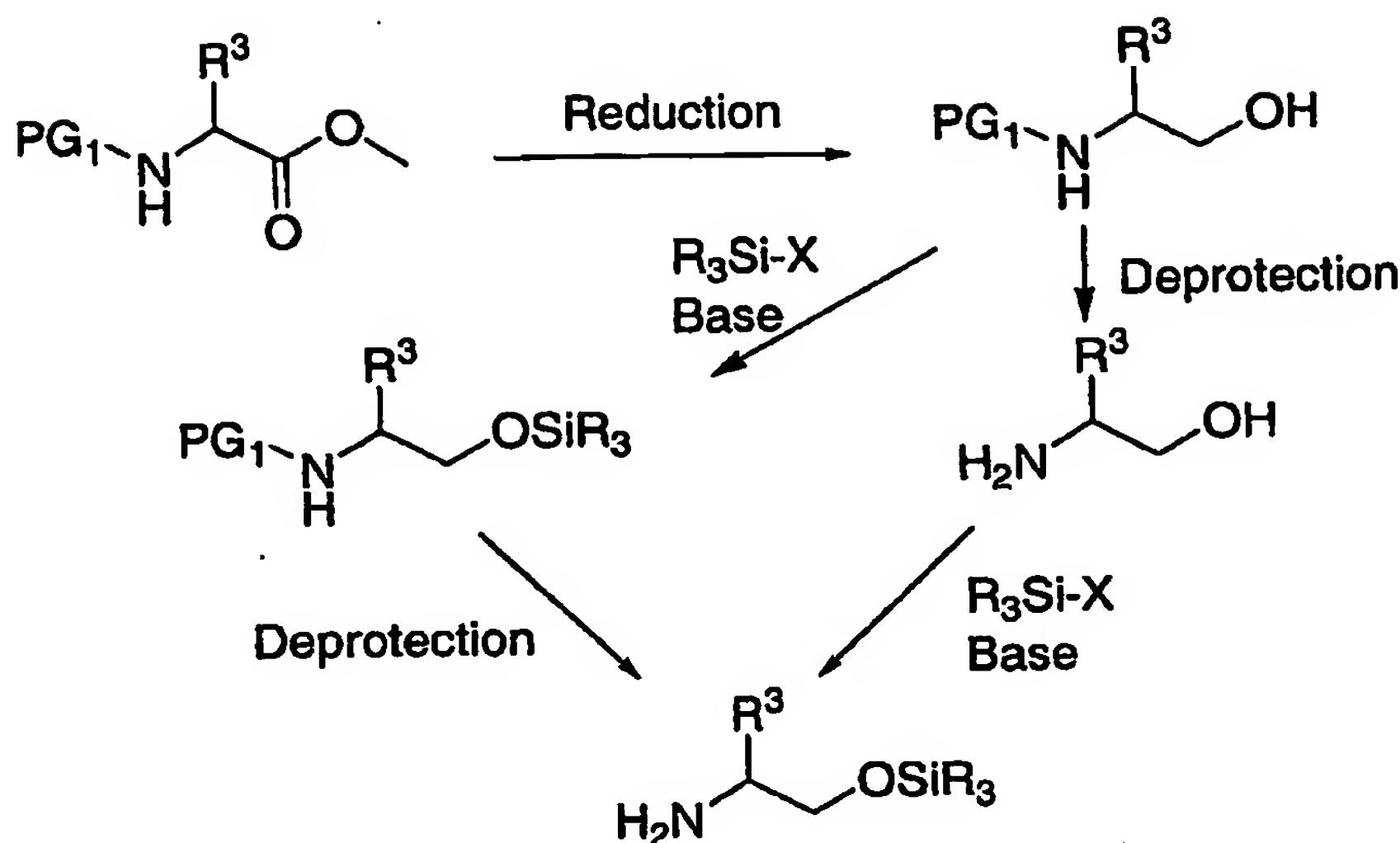
SCHEME 5



5 The amino alcohols used for the present invention may also be synthesized according to Scheme 6. A protected amino acid is reduced with a reducing agent such as NaBH_4 with or without an additive such as LiCl , in a solvent such as EtOH or a mixed solvent system such as EtOH/THF . The amino protecting group is then removed with the appropriate method according to the nature of the protecting group. The amino alcohol can then be silylated for use in Scheme 3.

10 Alternatively, the alcohol may be silylated prior to deprotection of the amine, followed by removal of an orthogonal amine protecting group.

SCHEME 6

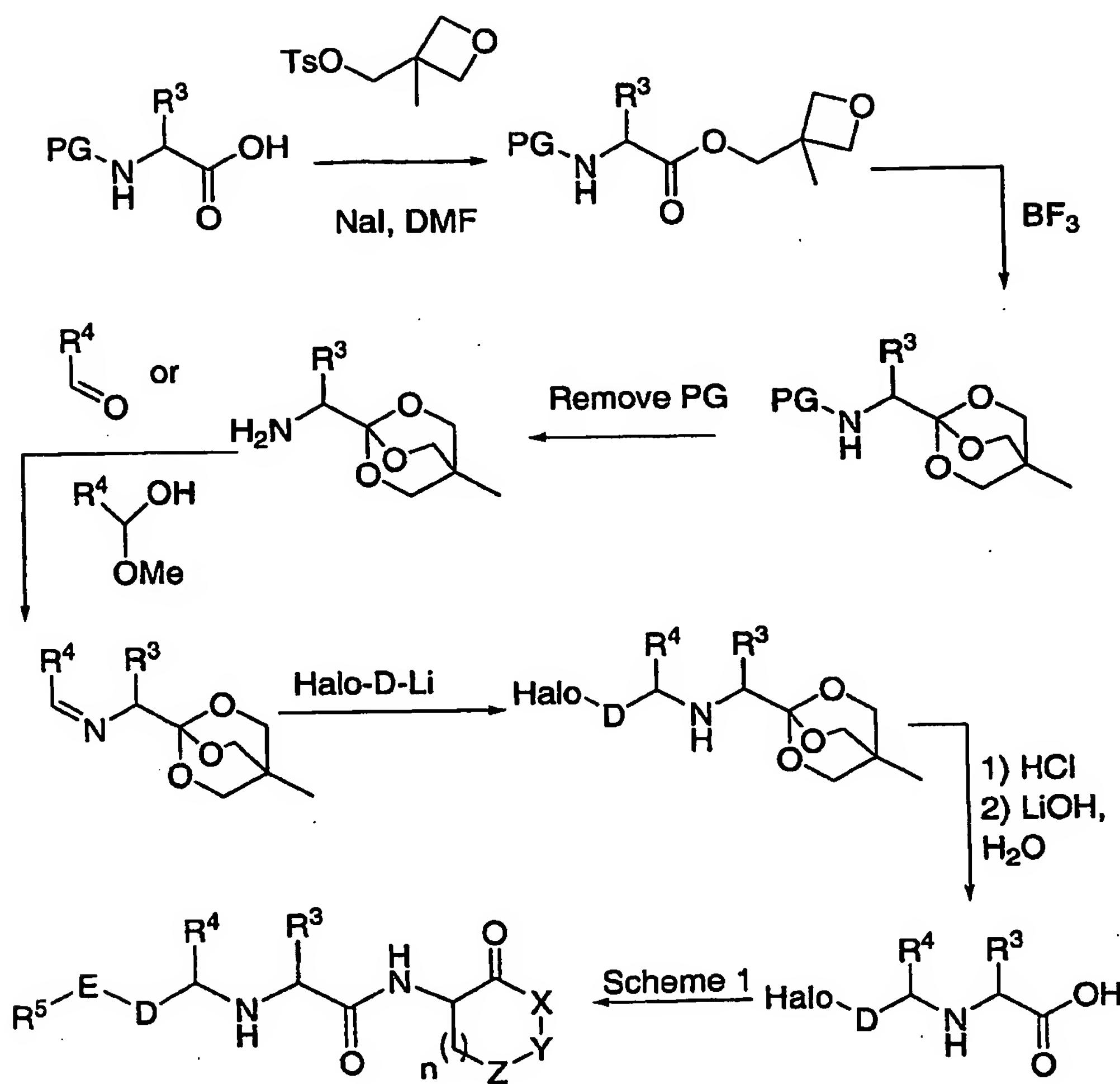


5 Compounds of the current invention may also be prepared according to Scheme 7, as shown below. Reaction of a suitably N-protected amino acid derivative with oxetane tosylate in the presence of sodium iodide in a suitable organic solvent such as dimethylformamide provides the corresponding oxetane ester which upon treatment with diborane provides the ortho ester.

10 Removal of the amino protecting group affords an amine which upon condensation with an aldehyde of formula $R^4\text{CHO}$ or a hemiacetal of formula $R^4\text{C}(\text{OH})(\text{OR})$ (where R is an alkyl group) under the reaction conditions described above provides an imine. Treatment of the imine with a Grignard or organolithium reagent under the reaction conditions described above provides an N-alkylated derivative. Removal of the ortho ester provides the corresponding carboxylic acid which is then converted into compounds of the current invention as described in Scheme 1.

15

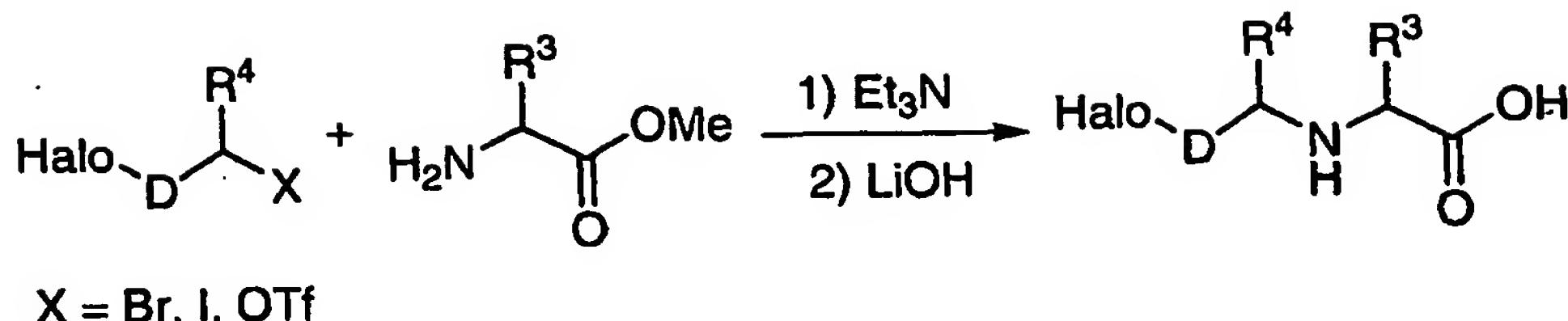
SCHEME 7



5

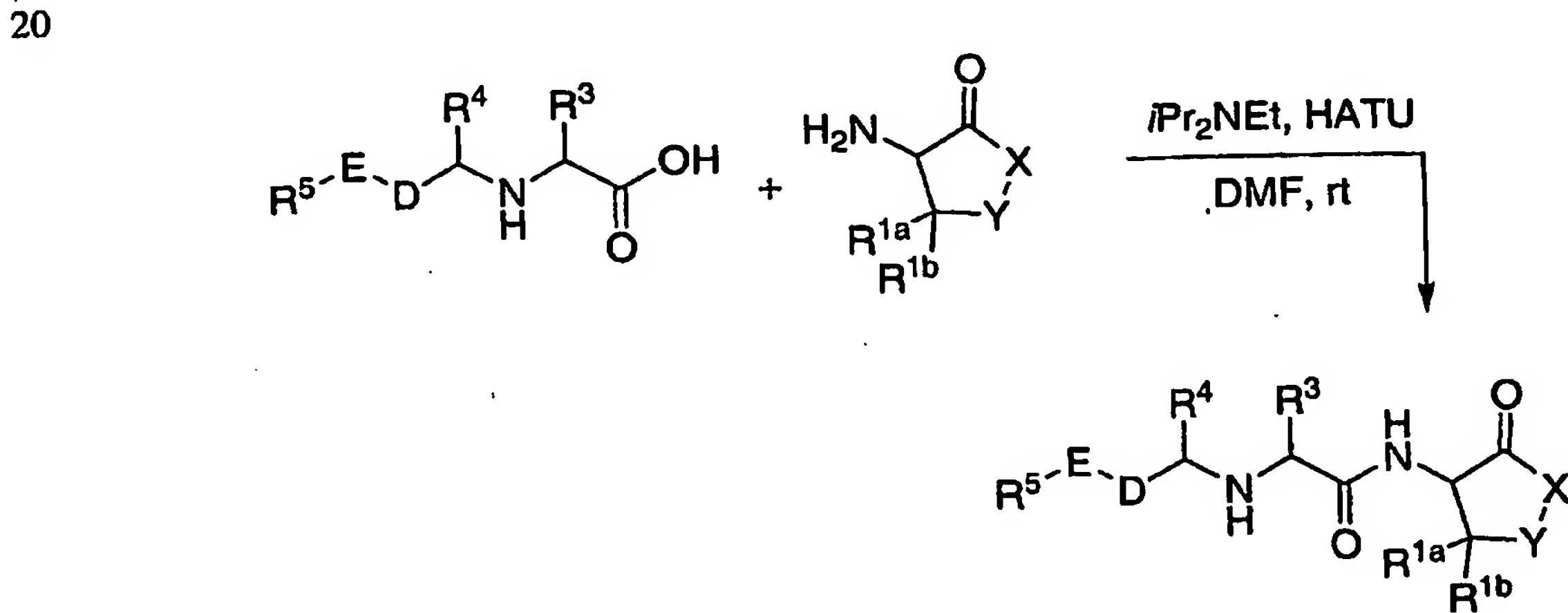
Carboxylic acids of the form $\text{Halo-D-CH}(\text{R}^4)\text{NHCH}(\text{R}^3)\text{COOH}$ shown in Schemes 1, 2, and 7 may also be prepared as shown in Scheme 8. An appropriately substituted benzyl bromide, iodide or triflate (which may be chiral or racemic) may be coupled with an alpha amino ester under basic conditions. Hydrolysis with aqueous base then provides the acid which can be converted into examples of the current invention.

SCHEME 8



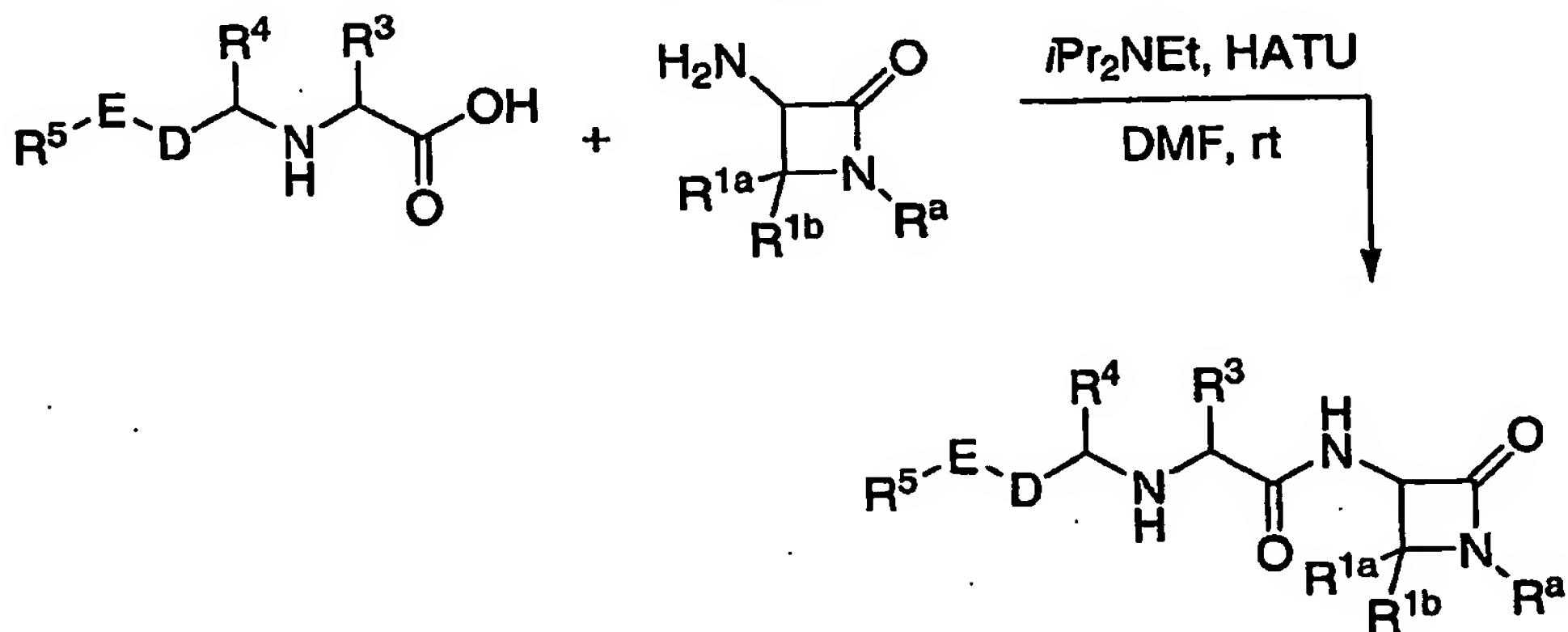
Compounds of the present invention can be prepared by coupling a suitable N-substituted amino acid to an appropriate α -amino- γ -butyrolactone ($X=O$, $Y=CH_2$ $R_{1a}=R_{1b}=H$ is commercially available; for $X=O$, $Y=C(CH_3)_2$, $R_{1a}=R_{1b}=H$, see Fillman, J.; Albertson, N. *J. Am. Chem. Soc.* 1948, 70, 171-174; for $X=O$, $Y=CH_2$, $R_{1a}=R_{1b}=CH_3$, see Holly, F. W.; Barnes, R. A.; Koniuszy, F. R.; Folkers, K. *J. Am. Chem. Soc.* 1948, 70, 3088-3090) or alternatively to an appropriate 3-amino-2-pyrrolidinone ($X=NH$, $Y=CH_2$, $R_{1a}=R_{1b}=H$ is commercially available; for $X=NR_a$, $R_a=SO_2R_b$ (R_b =aryl or heteroaryl), $Y=CH_2$, $R_{1a}=R_{1b}=H$ see Poduska and Rudinger *Collect. Czech. Chem. Commun.* 1959, 24, 3449-3458; for $X=NH$, $Y=CHSO_2R_a$ (R_a =aryl or heteroaryl), $R_{1a}=R_{1b}=H$ see Boyd, D. B.; Elzey, T. K.; Hatfield, L.D.; Kinnick, M. D.; Morin Jr., J. M. *Tetrahedron Lett.* 1986, 27, 3453-3456; for $X=NR_a$, $R_a=H$, $Y=CO$, $R_{1a}=R_{1b}=H$ see Liotta, L. J.; Gibbs, R. A.; Taylor, S. D.; Benkovic, P. A.; Benkovic, S. J. *J. Am. Chem. Soc.* 1995, 117, 4729-4741; for $X=NR_a$, $Y=SO_2$, $R_{1a}=R_{1b}=H$ see Chen, Z.; Demuth Jr., T. P.; Wireko, F. C.; *Bioorg. Med. Chem. Lett.* 2001, 11, 2111-2115) as shown in Scheme 9.

SCHEME 9



Compounds of the present invention can also be prepared by coupling a suitable N-substituted amino acid to an appropriate α -amino- β -lactam (for $R_a=R_{1a}=R_{1b}=H$ or $R_a=OCH_3$, $R_{1a}=R_{1b}=H$ see Floyd, D. M.; Fritz, A.W.; Pluscec, J.; Weaver, E. R.; Cimarusti, C. M. *J. Org. Chem.* 1982, 47, 5160-5167; for $R_a=R_{1a}=H$, $R_{1b}=OAc$ or $R_a=R_{1a}=H$, $R_{1b}=SR_b$ or SO_2R_b (R_b =aryl or heteroaryl) see Zhou, N. E.; Guo, D.; Thomas, G.; Reddy, A. V. N.; Kaleta, J.; Purisima, E.; Menard, R.; Micetich, R. G.; Singh, R. *Biorg. Med. Chem. Lett.* 2003, 13, 139-141) according to Scheme 10.

SCHEME 10

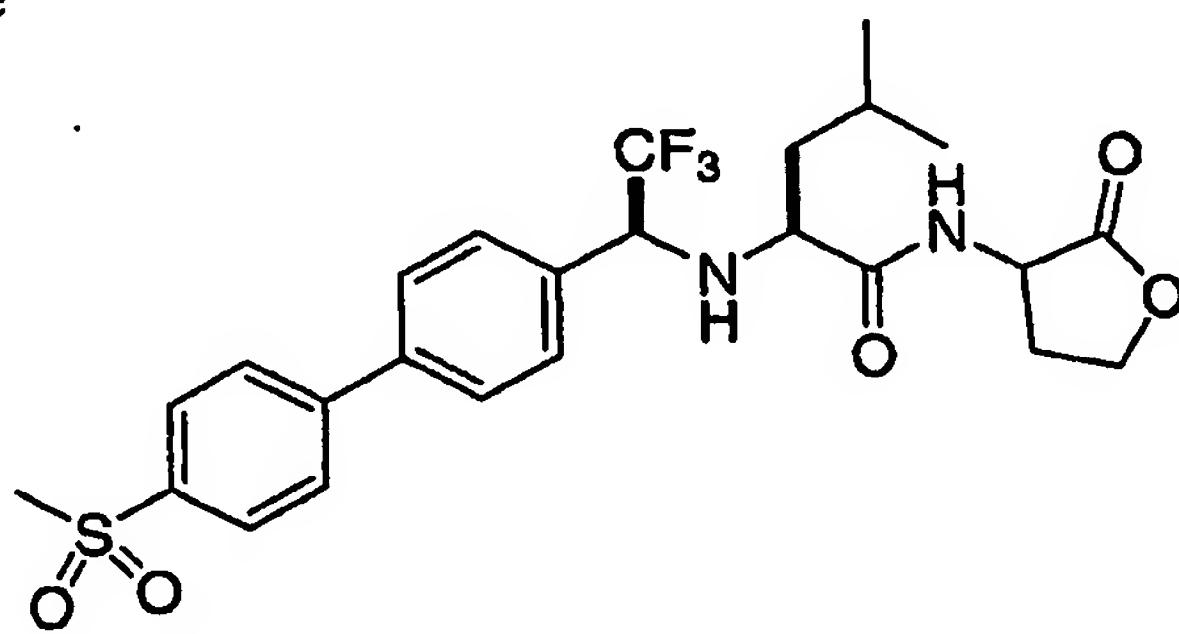


10

EXAMPLE 1

*N*¹-(2-oxotetrahydrofuran-3-yl)-*N*²-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide

15



Triethylamine (30 μ L, 220 μ mol) was added to a solution of *N*-(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl-L-leucine (30 mg, 68 μ mol), benzotriazol-1-yl-

oxytritypyrrolidinophosphonium hexafluorophosphate (40 mg, 77 μ mol) and α -amino- γ -

20 butyrolactone hydrobromide (26 mg, 140 μ mol) in DMF (0.20 mL) with stirring at rt for 30

minutes. The mixture was then partitioned between ethyl acetate and water and the layers separated. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated and the residue was purified by flash chromatography on silica gel eluting with ethyl acetate to afford the title compound as a colorless solid MS(+ESI): 527.2 $[\text{M}+1]^+$.

5

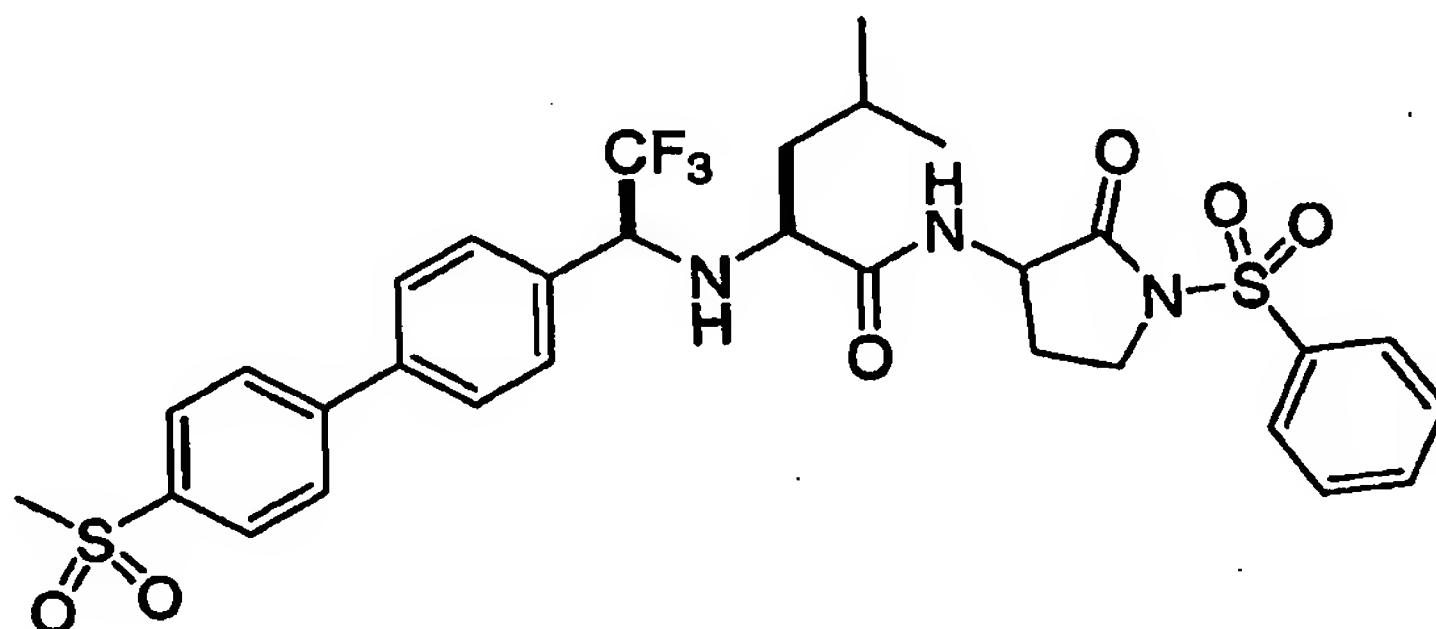
^1H NMR (acetone- d_6 , 500 MHz) δ 8.06 (4H, d), 8.00-7.95 (4H, m), 7.90 (1H, m), 7.83 (1H, overlapped m), 7.80 (4H, d), 7.67 (4H, t), 4.58 (2H, m), 4.45 (2H, m), 4.37 (2H, m), 4.27 (2H, m), 3.53 (2H, m), 3.19 (6H, s), 2.83 (2H, m), 2.50 (2H, m), 2.20 (2H, m), 1.95 (2H, m), 1.53 (4H, m), 0.95 (12H, d).

10

EXAMPLE 2

*N*¹-[2-oxo-1-(phenylsulfonyl)pyrrolidin-3-yl]-*N*²-{(1*S*)-2,2,2-trifluoro-1-[4'-
(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide

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Triethylamine (30 μL , 220 μmol) was added to a solution of *N*-(1*S*)-2,2,2-trifluoro-1-[4'-
(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucine (40 mg, 90 μmol), benzotriazol-1-yl-
oxytritypyrrolidinophosphonium hexafluorophosphate (55 mg, 110 μmol) and (54 mg, 220 μmol)
in DMF (0.20 mL) with stirring at rt for 2.5 h. The mixture was then partitioned between ethyl
acetate and water and the layers separated. The organic phase was washed with brine, dried
(Na_2SO_4) and concentrated and the residue was purified by flash chromatography on silica gel
eluting with 3/2 ethyl acetate/hexanes to afford the title compound as a colorless thick syrup
MS(+ESI): 666.3 $[\text{M}+1]^+$.

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^1H NMR (acetone- d_6 , 500 MHz) δ 8.07-7.97 (8H, m), 7.96-7.92 (4H, m), 7.86-7.70 (8H, m),
7.65-7.57 (8H, m), 4.54 (2H, m), 4.40 (2H, m), 3.93 (2H, m), 3.80 (2H, m), 3.66 (2H, m), 3.45
(2H, m), 3.18 (6H, s), 2.35 (2H, m), 2.00-1.80 (4H, m), 1.45 (4H, m), 0.89 (12H, d).

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Pharmaceutical Composition

As a specific embodiment of this invention, 100 mg of *N*¹-(2-oxotetrahydrofuran-3-yl)-*N*²-{(1*S*)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to 5 fill a size 0, hard-gelatin capsule.

The compounds disclosed in the present application exhibited activity in the following assays. In addition, the compounds disclosed in the present application have an enhanced pharmacological profile relative to previously disclosed compounds.

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Cathepsin K Assay

Serial dilutions (1/3) from 500 μ M down to 0.0085 μ M of test compounds were prepared in dimethyl sulfoxide (DMSO). Then 2 μ L of DMSO from each dilution were added to 50 μ L of assay buffer (MES, 50 mM (pH 5.5); EDTA, 2.5 mM; DTT, 2.5 mM and 10% DMSO) 15 and 25 μ L of human cathepsin K (0.4 nM) in assay buffer solution. The assay solutions were mixed for 5-10 seconds on a shaker plate and incubated for 15 minutes at room temperature. Z-Leu-Arg-AMC (8 μ M) in 25 μ L of assay buffer was added to the assay solutions. Hydrolysis of 20 the coumarin leaving group (AMC) was followed by spectrofluorometry (Ex λ =355 nm; Em λ = 460 nm) for 10 minutes. Percent of inhibition were calculated by fitting experimental values to standard mathematical model for dose response curve.

Cathepsin L Assay

Serial dilutions (1/3) from 500 μ M down to 0.0085 μ M of test compounds were prepared in dimethyl sulfoxide (DMSO). Then 2 μ L of DMSO from each dilution were added to 50 μ L of assay buffer (MES, 50 mM (pH 5.5); EDTA, 2.5 mM; DTT, 2.5 mM and 10% DMSO) 25 and 25 μ L of human cathepsin L (0.5 nM) in assay buffer solution. The assay solutions were mixed for 5-10 seconds on a shaker plate and incubated for 15 minutes at room temperature. Z-Leu-Arg-AMC (8 μ M) in 25 μ L of assay buffer was added to the assay solutions. Hydrolysis of 30 the coumarin leaving group (AMC) was followed by spectrofluorometry (Ex λ =355 nm; Em λ = 460 nm) for 10 minutes. Percent of inhibition were calculated by fitting experimental values to standard mathematical model for dose response curve.

Cathepsin B Assay

Serial dilutions (1/3) from 500 μ M down to 0.0085 μ M of test compounds were prepared in dimethyl sulfoxide (DMSO). Then 2 μ L of DMSO from each dilution were added to 35

50 μ L of assay buffer (MES, 50 mM (pH 5.5); EDTA, 2.5 mM; DTT, 2.5 mM and 10% DMSO) and 25 μ L of human cathepsin B (4.0 nM) in assay buffer solution. The assay solutions were mixed for 5-10 seconds on a shaker plate and incubated for 15 minutes at room temperature. Z-Leu-Arg-AMC (8 μ M) in 25 μ L of assay buffer was added to the assay solutions. Hydrolysis of the coumarin leaving group (AMC) was followed by spectrofluorometry (Ex λ =355 nm; Em λ = 460 nm) for 10 minutes. Percent of inhibition were calculated by fitting experimental values to standard mathematical model for dose response curve.

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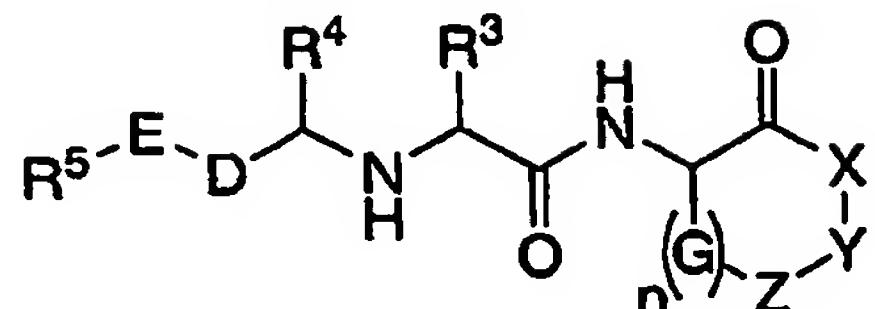
Cathepsin S Assay

10 Serial dilutions (1/3) from 500 μ M down to 0.0085 μ M of test compounds were prepared in dimethyl sulfoxide (DMSO). Then 2 μ L of DMSO from each dilution were added to 50 μ L of assay buffer (MES, 50 mM (pH 5.5); EDTA, 2.5 mM; DTT, 2.5 mM and 10% DMSO) and 25 μ L of human cathepsin S (20 nM) in assay buffer solution. The assay solutions were 15 mixed for 5-10 seconds on a shaker plate and incubated for 15 minutes at room temperature. Z-Leu-Arg-AMC (8 μ M) in 25 μ L of assay buffer was added to the assay solutions. Hydrolysis of the coumarin leaving group (AMC) was followed by spectrofluorometry (Ex λ = 355 nm; Em λ = 460 nm) for 10 minutes. Percent of inhibition were calculated by fitting experimental values to standard mathematical model for dose response curve.

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WHAT IS CLAIMED IS:

1. A compound of the formula:



5 wherein X is O or -NR⁹;
Y is CR¹R², -SO₂, C=O or -NR⁹;
Z is CR¹R², O, S, -SO₂ or -NR⁹;
Each G is independently CR¹R²;

10 R¹ is hydrogen, halo, or C₁₋₆ alkyl which is optionally substituted with one, two, or three substituents independently selected from halo or -OR⁸;

R² is hydrogen, halo or C₁₋₆ alkyl which is optionally substituted with one, two, or three substituents independently selected from halo or -OR⁸;

15 or R¹ and R² can be taken together with the carbon atom to which they are attached to form a C₃₋₈ membered ring which is optionally substituted with one or two substituents independently selected from C₁₋₆ alkyl, halo or keto;

R³ is C₁₋₆ alkyl or C₂₋₆ alkenyl, wherein said alkyl and alkenyl groups are optionally substituted with C₃₋₆ cycloalkyl, aryl, heteroaryl or one to six halo;

20 R⁴ is C₁₋₆ alkyl substituted with 1-6 halo;

D is aryl or heteroaryl, wherein said aryl or heteroaryl group, which may be monocyclic or 25 bicyclic, is optionally substituted on either the carbon or the heteroatom with one to five substituents independently selected from C₁₋₆ alkyl, haloalkyl, halo, keto, alkoxy, -SR⁶, -OR⁶, N(R⁶)₂ or -SO₂R⁶

E is aryl or heteroaryl, wherein said aryl or heteroaryl group, which may be monocyclic or 30 bicyclic, is optionally substituted on either the carbon or the heteroatom with one to five substituents independently selected from C₁₋₆ alkyl, haloalkyl, halo, keto, alkoxy, -SR⁶, -OR⁶, N(R⁶)₂ or -SO₂R⁶;

R₅ is hydrogen, C₁₋₆ alkyl, C₁₋₆ alkyloxy, aryl, heteroaryl, C₃₋₈ cycloalkyl, heterocyclyl, -OR₆, -C(O)R₆, -R⁷C(O)R₆, -C(O)N(R^a)(R^b), -C(O)N(R⁹)(R⁹), -C(R⁷)(R⁸)OH, R⁷SR₆, -C(R^a)(R^b)N(R₆)₂, C(R^a)(R^b)N(R^a)(R^b), -NR⁷C(O)NR⁷S(O)R₆, -SO_mR₆, -SO₂N(R^a)(R^b), -SO₂N(R⁷)C(O)(R⁹), -SO₂(R⁷)C(O)N(R⁹)₂, -N(R⁷)C(O)N(R⁷)(R⁶), -N(R⁷)C(O)R₆, -N(R⁷)C(O)OR₇, -N(R⁷)SO₂(R⁷), -C(R^a)(R^b)SC(R^a)(R^b)(R⁶), -C(R^a)(R^b)NR⁷C(R^a)(R^b)(R⁶), -C(R^a)(R^b)NH₂, -C(R^a)(R^b)C(R^a)(R^b)N(R^a)(R^b), -C(O)C(R^a)(R^b)N(R^a)(R^b), -C(R^a)(R^b)N(R₆)C(O)R₆, -C(R^a)(R^b)C(O)N(R^a)(R^b), wherein said groups are optionally substituted on either the carbon or the heteroatom with one to five substituents independently selected from C₁₋₆ alkyl, halo, keto, cyano, haloalkyl, hydroxyalkyl, -OR₆, -NO₂, -NH₂, -NHS(O)R₈, -R₆SO₂R⁹, -SO_mR⁷, heterocyclyl, aryl, or heteroaryl;

R₆ is selected from hydrogen, C₁₋₆ alkyl, aryl, aryl(C₁₋₄)alkyl, heteroaryl, heteroaryl(C₁₋₄)alkyl, C₃₋₈cycloalkyl, C₃₋₈cycloalkyl(C₁₋₄)alkyl, and heterocyclyl(C₁₋₄)alkyl wherein said groups can be optionally substituted with one, two, or three substituents independently selected from halo, alkoxy, cyano, -NR^aR^b, -SR^a or -SO_mR^a;

R⁷ is hydrogen or C₁₋₆ alkyl;

R⁸ is hydrogen or C₁₋₆ alkyl;

R⁹ is hydrogen, C₁₋₆ alkyl, C(O)R⁷, C(O)C₁₋₆ alkyl, C(O)aryl, C(O)heteroaryl, C(O)C₁₋₆ alkoxy, SO₂(C₁₋₆ alkyl), SO₂(aryl) or SO₂(heteroaryl), wherein said alkyl groups are optionally substituted with one, two, or three substituents independently selected from halo, alkoxy, cyano, -NR⁷ or -SR⁷;

R^a is hydrogen or C₁₋₆ alkyl which is optionally substituted with one, two, or three substituents independently selected from halo or -OR₆;

R^b is hydrogen or C₁₋₆ alkyl which is optionally substituted with one, two, or three substituents independently selected from halo or -OR₆;

or R^a and R^b can be taken together with the nitrogen atom to which they are attached or are between them to form a C₃₋₈ heterocyclyl ring which is optionally substituted with one or two substituents independently selected from C₁₋₆ alkyl, halo hydroxyalkyl, hydroxy, alkoxy or keto;

n is an integer from zero to two;
m is an integer from zero to two;
or a pharmaceutically acceptable salt or stereoisomer thereof.

5 2. The compound of Claim 1 wherein R³ is C₁₋₆ alkyl optionally substituted with one to six halo.

10 3. The compound of Claim 2 wherein D is aryl.

10 4. The compound of Claim 3 wherein D is phenyl.

15 5. The compound of Claim 2 wherein E is aryl or heteroaryl, wherein said aryl or heteroaryl group is optionally substituted on either the carbon or the heteroatom with one to five halo.

15 6. The compound of Claim 5 wherein E is phenyl or pyridyl, wherein said phenyl or pyridyl group may be substituted with one to five halo.

20 7. The compound of Claim 1 selected from

20 N¹-(2-oxotetrahydrofuran-3-yl)-N²-{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide;

25 N¹-[2-oxo-1-(phenylsulfonyl)pyrrolidin-3-yl]-N²-{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide;

25 N²-((1S)-1-{4'-(1-aminocarbonyl)cyclopropyl}biphenyl-4-yl)-2,2-difluoroethyl)-4-fluoro-N¹-

25 [(3S,4S)-2-oxo-4-(trifluoromethyl)pyrrolidin-3-yl]-L-leucinamide;

30 N²-((1S)-2,2-difluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]propyl)-4-fluoro-N¹-[(3S)-2-oxo-4-(trifluoromethyl)tetrahydrofuran-3-yl]-L-leucinamide;

30 N²-((1S)-1-{4'-(1-aminocarbonyl)cyclopropyl}biphenyl-4-yl)-2,2-difluoroethyl)-4-fluoro-N¹-[(3S,4S)-4-methyl-2-oxo-1-(pyridin-2-ylmethyl)pyrrolidin-3-yl]-L-leucinamide;

30 N²-((1S)-1-{4'-(1-aminocarbonyl)cyclopropyl}biphenyl-4-yl)-2,2-difluoroethyl)-N¹-[(3R)-4,4-difluoro-2-oxopyrrolidin-3-yl]-4-fluoro-L-leucinamide;

or a pharmaceutically acceptable salt or stereoisomer thereof.

8. N^1 -(2-oxotetrahydrofuran-3-yl)- N^2 -{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide, or a pharmaceutically acceptable salt or stereoisomer thereof.

5 9. N^1 -[2-oxo-1-(phenylsulfonyl)pyrrolidin-3-yl]- N^2 -{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)biphenyl-4-yl]ethyl}-L-leucinamide, or a pharmaceutically acceptable salt or stereoisomer thereof.

10 10. A pharmaceutical composition comprising a compound according to
Claim 1 and a pharmaceutically acceptable carrier.

11. A pharmaceutical composition made by combining a compound according to Claim 1 and a pharmaceutically acceptable carrier.

15 12. A process for making a pharmaceutical composition comprising
combining a compound according to Claim 1 and a pharmaceutically acceptable carrier.

20 13. A method of inhibiting cathepsin activity in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a compound according to Claim 1.

14. The method according to Claim 13 wherein the cathepsin activity is
Cathepsin K activity.

25 15. A method of treating or preventing a disease selected from: osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, atherosclerosis, obesity, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, metastatic bone disease, hypercalcemia of malignancy or multiple myeloma in a mammal in need thereof by
30 administering to the mammal a therapeutically effective amount of a compound according to Claim 1.

16. The method of Claim 15 wherein the disease is osteoporosis.

17. A method of treating cathepsin dependent conditions in a mammal in need thereof by administering to the mammal a therapeutically effective amount of a compound according to Claim 1.

5 18. A pharmaceutical composition comprising a compound of Claim 1 and another agent selected from: an organic bisphosphonate, an estrogen receptor modulator, an estrogen receptor beta modulator, an androgen receptor modulator, an inhibitor of osteoclast proton ATPase, an inhibitor of HMG-CoA reductase, an integrin receptor antagonist, or an anabolic agent, a selective cyclooxygenase-2 inhibitor, or a pharmaceutically acceptable salt or
10 mixture thereof.

15 19. A method of treating or preventing a disease selected from: osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, atherosclerosis, obesity, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, metastatic bone disease, hypercalcemia of malignancy or multiple myeloma comprising a compound of Claim 1 and another agent selected from: an organic bisphosphonate, an estrogen receptor modulator, an androgen receptor modulator, an inhibitor of osteoclast proton ATPase, an inhibitor of HMG-CoA reductase, an integrin receptor antagonist, or an osteoblast anabolic agent, a selective
20 cyclooxygenase-2 inhibitor, or a pharmaceutically acceptable salt or mixture thereof.

20. The method of Claim 19 wherein the disease is osteoporosis.

25 21. The method of Claim 19 wherein the disease is osteoarthritis.

22. A pharmaceutical composition comprising a compound of Claim 1 and another agent selected from: an organic bisphosphonate, an estrogen receptor modulator, an estrogen receptor beta modulator, an androgen receptor modulator, an inhibitor of osteoclast proton ATPase, an inhibitor of HMG-CoA reductase, an integrin receptor antagonist, or an
30 osteoblast anabolic agent, a selective cyclooxygenase-2 inhibitor, or pharmaceutically acceptable salt or mixture thereof.

35 23. A method of inhibiting bone resorption with a compound according to
Claim 1.

24. A method of increasing bone mineral density with a compound according to Claim 1.
25. A method of reducing the risk of fractures with a compound of Claim 1.

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ABSTRACT OF THE DISCLOSURE

This invention relates to a novel class of compounds which are cysteine protease inhibitors, including but not limited to, inhibitors of cathepsins K, L, S and B. These compounds are useful for treating diseases in which inhibition of bone resorption is indicated, such as
5 osteoporosis.